AMERICAN
HEART
JOURNAL

An international publication for the study of the circulation

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1430 Tulane Avenue, New Orleans 12, Louisiana

Published by The C. V. Mosby Company,
3207 Washington Boulevard, St. Louis 3, Mo.

VOLUME 58

JULY-DECEMBER, 1959

VOLUME 58

Printed in the
United States of America

AMERICAN HEART JOURNAL

July, 1959
Volume 58, No. 1

Clinical Communications

The Application of a Monoamine-Oxidase Inhibitor, 1-Phenyl-2-Hydrazinopropane (JB-516), to the Treatment of Primary Hypertension

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An interesting and frequently observed phenomenon in patients receiving iproniazid (Marsilid) has been the development of postural hypotension. This drug was the first monoamine-oxidase (MAO) inhibitor to be used clinically, initially as a tuberculostatic agent, more recently in the treatment of psychic depression and angina pectoris.[1,2] Some authors have also reported the drug to be useful in the therapy of hypertension.[1,3] Its further application has been limited, however, because of the inconsistency of the hypotensive response, the development of distressing side effects, and hepatic toxicity.

MAO is involved in the metabolism of several endogenous, physiologically active amines, including tryptamine, 5-hydroxytryptamine (serotonin), 3,4-dihydroxyphenylethylamine (dopamine), and norepinephrine. Thus, one might expect some alteration of cardiovascular dynamics to result from inhibition of this enzyme, and it seemed to us that inhibition of MAO might be a fundamental basis for hypotension such as was noted during the administration of iproniazid. Therefore, a program of study was instituted in hypertensive patients in order to screen various chemical agents for their ability to block MAO, while simultaneous observations were made to detect any alterations in the blood pressure.

This report concerns the first practical results of these investigations—the discovery of a new antihypertensive agent, 1-phenyl-2-hydrazinopropane (JB-516, Catron). This drug, the structure of which is shown in Fig. 1, is one of the most potent inhibitors of MAO presently available.[4-6] An initial evaluation of

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Received for publication Feb. 20, 1959.

this compound in the treatment of hypertension will be described, and some of the biochemical evidence which demonstrates the inhibition of MAO by JB-516 in man will be presented.

MATERIALS AND METHODS

The drug was supplied as 3.0, 6.25, 12.5, and 25 mg. tablets.* The results to be reported were obtained in 21 patients with persistent moderate to severe primary (essential) hypertension.

Nine of these patients were hospitalized and were subjects for short-term studies in which JB-516 was administered in a single daily dose of from 12.5 to 50 mg. for 12 to 25 days. Observations were made before, during, and after therapy. Blood pressures were determined four times each day in the recumbent and erect positions (after standing for 2 minutes). Serial electrocardiograms, tests of liver function, routine urinalyses, white blood cell counts, and hematocrits were obtained in order to detect possible toxic reactions. No medications other than cardiac glycosides and mild sedatives were permitted during the periods of study, and the salt intake was not restricted. The remaining 12 patients were observed in the outpatient clinic for from 50 to 150 days on therapy with JB-516 alone or in combination with chlorothiazide. All had severe hypertension, which in 7 patients had required the use of ganglionic blocking agents for adequate control. These patients either recorded their own blood pressures twice daily (lying and standing) or were hospital employees who had their blood pressures recorded each day by a nurse. They were followed initially at weekly intervals and later at 2-week intervals. At each clinic visit their blood pressures were measured by a physician, and a blood sample was obtained for white blood cell count, hematocrit, urea nitrogen, and serum transaminase.

The procedure used to demonstrate the inhibition of MAO consisted of the daily oral administration of 20 mg. of serotonin and the measurement of the per cent of conversion of the amine to its MAO metabolite, 5-hydroxyindoleacetic acid (5-HIAA).[6] The conversion percentage, which decreases with inhibition of MAO, is established by assaying 5-HIAA in urine collected for 8 hours after administration of the amine.

RESULTS

When this study was begun, there was no available information on the optimal schedule of dosage for JB-516, and its effect on human blood pressure was unknown. It was soon apparent that the drug was a potent orthostatic hypotensive agent, and that cumulative action occurred even with a single daily dose. Thus, while therapy was initiated with 25 mg. per day, in many cases a downward adjustment of dosage became necessary within 1 to 2 weeks.

Alterations in Blood Pressure.—The effect of JB-516 on recumbent and standing blood pressures in the 9 hospitalized patients is summarized in Figs. 2 and 3. A slight decrease in the blood pressure in the recumbent position was noted in Patients No. 1, 3, and 8, but marked lowering of the blood pressure in the upright position developed in 8 of these 9 patients. Patient No. 4 failed to respond to a daily dose of from 25 to 50 mg. during a 21-day period of therapy. The type of response seen in the remaining 8 patients is illustrated in Fig. 4. In this group of patients the onset of orthostatic lowering of the blood pressure occurred from 3 to 14 days after the beginning of therapy. Following the cessation of therapy, the standing blood pressure began to rise within 24 to 48 hours, but usually 7 to 15 days elapsed before it returned to control levels in both the recumbent and standing positions.

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*Courtesy of Dr. H. Dalell, Lakeside Laboratories, Milwaukee, Wis.

To simplify the presentation of results in the 12 clinic patients, the average blood pressures during the fourth and final weeks of therapy were selected arbitrarily for comparison with the average control blood pressures obtained during the week prior to institution of therapy with JB-516. The severity of the hypertension in several patients was such that discontinuance of all previous medications (see footnote, Table I) prior to the administration of JB-516 would have been hazardous. Thus, "control" values in some cases represent the patient's status on other drug regimens. These data, as well as the dosages of JB-516 and chlorothiazide are listed in Table I.

During the fourth week of study, 5 patients were receiving JB-516 alone and 7 patients were receiving a combined regimen of JB-516 and chlorothiazide. A definite orthostatic lowering was noted in 10 patients. One patient (L.N.), receiving JB-516 alone, responded with a significant lowering of both the recumbent and standing blood pressures as compared to control values, and 1 patient (E.J.) failed to respond to JB-516 and chlorothiazide in combination.

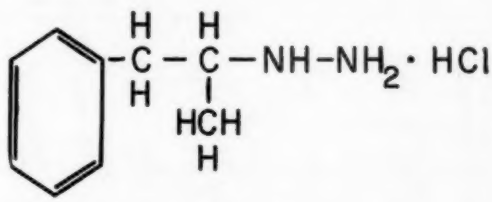

Fig. 1.—Chemical structure of JB-516.

Subsequently, chlorothiazide was discontinued in all patients except W.L. and E.J., in order to obtain information on relatively long-term management with JB-516 alone. A persistent orthostatic effect was noted during the final week of the study in 9 patients. Three patients (L.N., P.A., and W.L.) showed little orthostatic effect, since both the recumbent and standing blood pressure levels were reduced well below control values. Patient E.J. continued to be unresponsive.

Thus, it is apparent that the administration of JB-516 causes an orthostatic lowering of the blood pressure in most cases, and a recumbent lowering as well in a few patients. It is also our impression that generally lower recumbent and standing blood pressures are seen in patients receiving JB-516 in combination with chlorothiazide than in those receiving JB-516 alone.

A more detailed account of one patient's (S.Y.) clinical course over a period of 90 days is shown in Fig. 5. Prior to the administration of JB-516, it was necessary to use a combination of reserpine, hydralazine, mecamylamine, and chlorothiazide in order to obtain adequate blood pressure control. Reserpine and mecamylamine were discontinued at the time the administration of JB-516 was initiated, and hydralazine was discontinued shortly thereafter. Chlorothiazide was stopped on the forty-eighth day of the study, and the standing blood pressure continued to be controlled adequately on 6.25 to 12.5 mg. of JB-516 daily.

Other Effects.—None of the parasympathetic blocking effects ordinarily associated with the use of ganglionic blocking drugs were observed with JB-516.

Table I. Therapeutic Results With JB-516 in Twelve Clinic Patients. Weekly Average Supine and Standing Blood Pressures (mm. Hg) During Control Week, Fourth Week of Therapy, and Final Week of Therapy

Patient, age and sex	Duration of therapy (days)	Control*		Fourth week		Therapy during fourth week	Final week		Therapy during final week
		Supine	Standing	Supine	Standing		Supine	Standing	
F.D., 47, F	100	162/109	169/113	198/121	125/89	JB-516, 6.25-12.5 mg./day	206/129	141/110	JB-516, 12.5 mg./day
E.H., 57, F	120	203/120	171/120	199/112	136/100	JB-516, 6.25-12.5 mg./day Chlorothiazide, 1,000 mg./day	214/135	158/121	JB-516, 18.75-25 mg./day
T.H., 56, M	100	182/106	174/109	182/106	138/100	JB-516, 12.5 mg./day Chlorothiazide, 500 mg./day	202/114	155/110	JB-516, 12.5-25 mg./day
E.M., 46, F	160	181/119	166/118	172/113	138/101	JB-516, 25 mg./day	166/110	143/102	JB-516, 25 mg./day
B.T., 40, F	160	188/110	169/111	173/102	141/93	JB-516, 25 mg./day	185/110	166/108	JB-516, 25 mg./day
M.T., 34, M	150	173/119	158/120	167/109	147/102	JB-516, 25 mg./day	174/134	148/114	JB-516, 25 mg./day
S.Y., 46, M	140	183/119	115/106	178/119	140/93	JB-516, 12.5 mg./day Chlorothiazide, 500 mg./day	201/122	138/97	JB-516, 6.25-12.5 mg./day
L.N., 48, F	130	180/106	173/109	154/93	155/92	JB-516, 25 mg./day	160/90	157/92	JB-516, 25 mg./day
P.A., 62, F	150	250/119	241/119	193/96	177/78	JB-516, 25 mg./day Chlorothiazide, 1,000 mg./day	206/87	192/91	JB-516, 25 mg./day
W.L., 42, F	130	238/125	227/121	159/112	134/90	JB-516, 12.5 mg./day Chlorothiazide, 500 mg./day	196/111	182/108	JB-516, 12.5 mg./day Chlorothiazide, 500 mg./day
H.G., 45, F	145	225/147	221/148	185/131	161/118	JB-516, 6.25 mg./day Chlorothiazide, 1,000 mg./day	195/137	174/125	JB-516, 25 mg./day
E.J., 30, M	50	203/106	204/112	158/105	162/111	JB-516, 12.5 mg./day Chlorothiazide, 500 mg./day	170/117	154/123	JB-516, 12.5 mg./day Chlorothiazide, 1,000 mg./day

*The control period represents either a period of no therapy or a period of therapy with other antihypertensive agents as follows: Patient F.D.: mecamylamine, hydralazine, and reserpine. Patient E.H.: mecamylamine and chlorothiazide. Patient T.H.: mecamylamine, hydralazine, and chlorothiazide. Patient S.Y.: mecamylamine, reserpine, hydralazine, and chlorothiazide. Patient P.A.: mecamylamine and chlorothiazide. Patient H.G.: mecamylamine and chlorothiazide. Patient E. J.: reserpine and chlorothiazide.

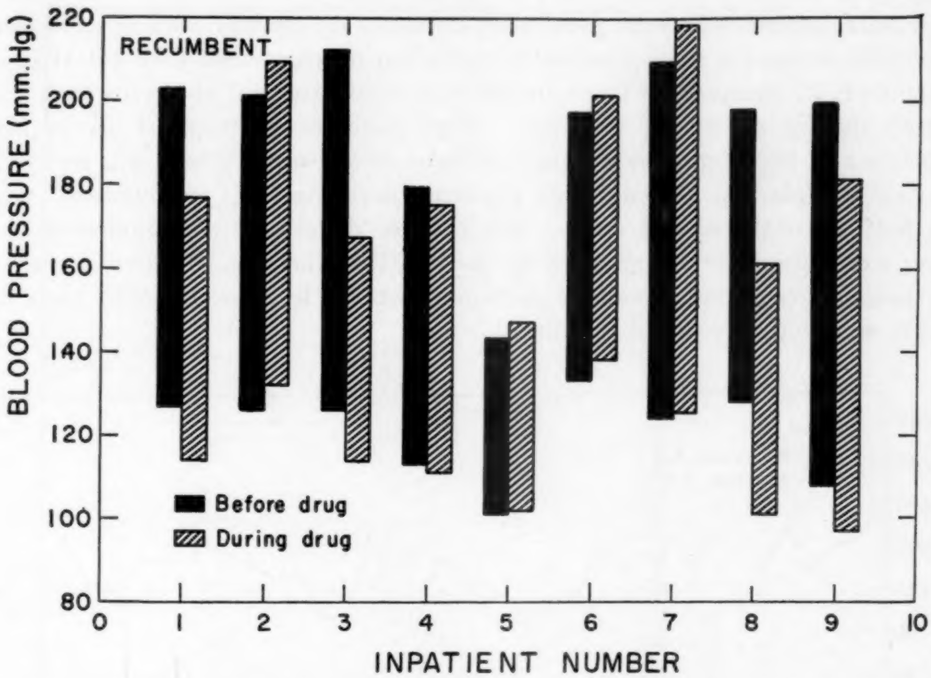

Fig. 2.—Average recumbent blood pressures (systolic and diastolic) before and during short-term therapy with JB-516.

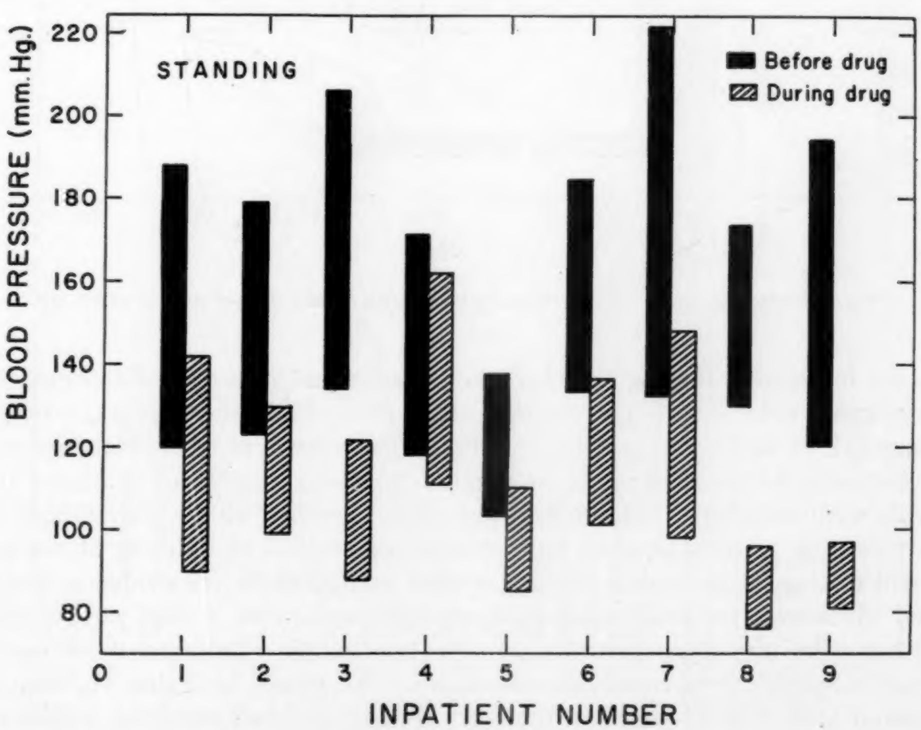

Fig. 3.—Average standing (2 minutes) blood pressures (systolic and diastolic) before and during short-term therapy with JB-516.

Two male patients who were previously impotent on therapy with mecamylamine were able to resume normal sexual activity during treatment with JB-516. One patient (E.J.) complained of an inability to ejaculate, but this symptom disappeared during continued therapy. Most patients experienced an improved appetite and had a moderate gain in weight as a result. There was no obvious psychic stimulation, although one patient complained of "nervousness" during the first few days of the study, and another developed tremulousness of the lower extremities for a few days at the onset of therapy. Otherwise, none of the patients exhibited insomnia or neuromuscular hyperexcitability as is commonly seen with the use of iproniazid.

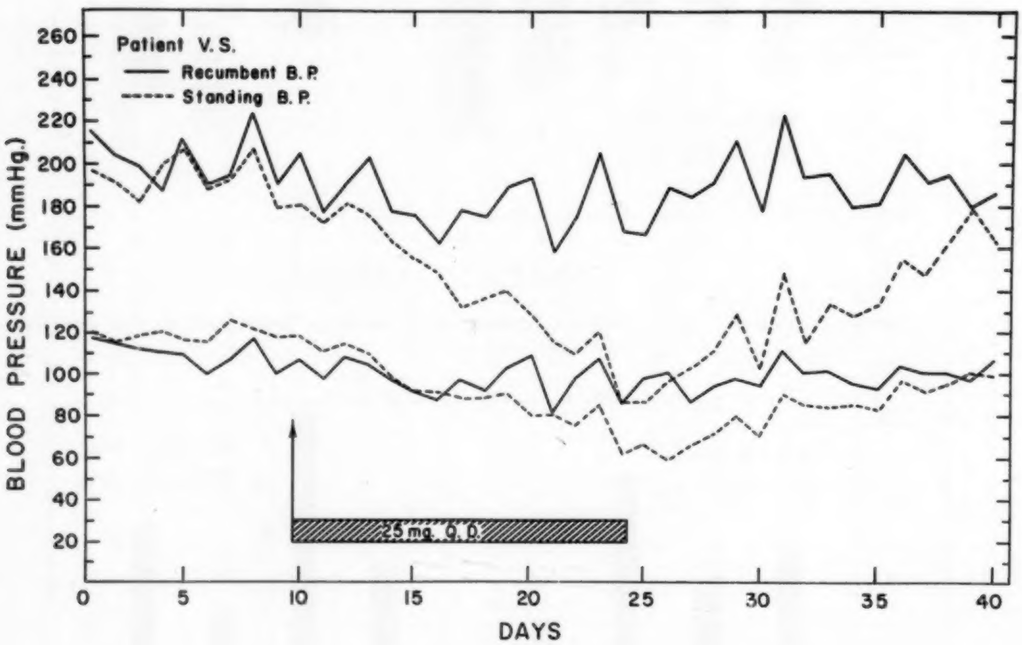

Fig. 4.—Orthostatic decrease in blood pressure with a daily dose of 25 mg. of JB-516.

An interesting finding has been the development of a reversible impairment of red-green color discrimination in 6 clinic patients during periods of maximal dosage (18.75 to 25 mg. per day). This impairment was of such a degree that the patients volunteered such information as being unable to interpret traffic signals with certainty. The defect was easily demonstrable with Ishihara color chart testing. Although each patient also complained of blurring of vision, on careful testing by the ophthalmologist there was no objective evidence of diminished visual acuity, and visual field examinations were within normal limits. Neither were any abnormalities seen on fundiscopic examination, except previously observed hypertensive retinopathy. As shown in Table II, this effect occurred after 3 to 23 weeks of therapy. Partial reversal occurred within a few days after cessation of therapy, but usually several weeks elapsed before there was complete restoration of normal color vision. Four of these patients were

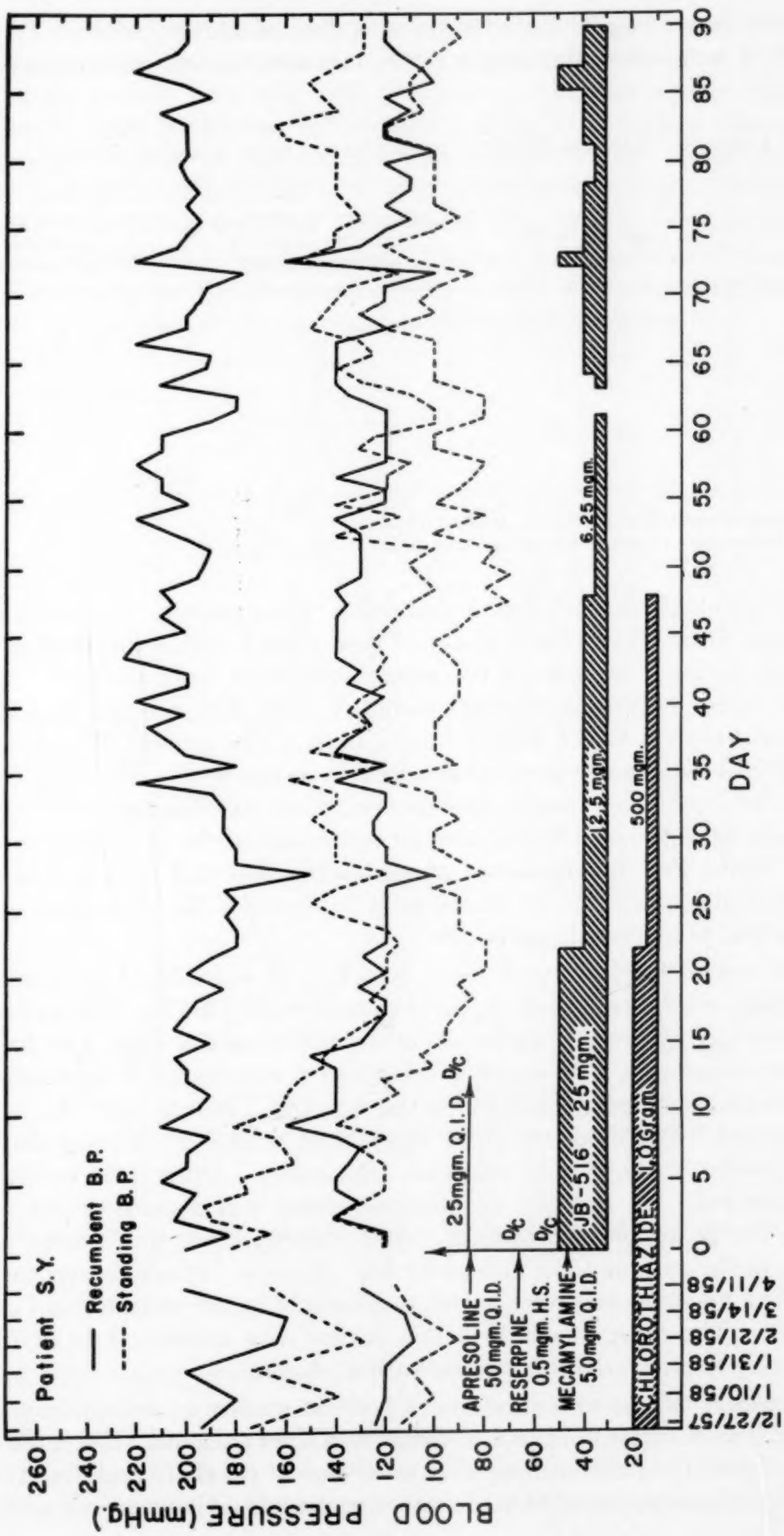

Fig. 5.—Long-term management of a case of severe hypertension.

subsequently treated again with JB-516 at a dose of 12.5 mg. daily. In only 1 patient (E.M.) did the color defect recur, necessitating discontinuation of the drug again.

TABLE II. FACTORS RELATED TO THE DEVELOPMENT OF COLOR DEFECT

PATIENT	DOSE OF JB-516 (MG./DAY)	DURATION OF THERAPY PRIOR TO ONSET OF DEFECT (WEEKS)	DURATION OF DEFECT AFTER STOPPING JB-516 (WEEKS)
P.A.*	25	21	5
B.T.	25	23	4½
E.M.*	25	23	3
	(12.5)†	(4)†	(2)†
W.L.	25	3	3
E.H.*	18.75–25	17	4
S.Y.*	25	20	5

*Subsequently restarted on JB-516, 12.5 mg. per day.
†These values refer to recurrence of the color defect in this patient.

One patient (P.A.) developed detectable abnormalities of liver function after therapy with JB 516 for 1 week. These abnormalities consisted of a rise in the serum glutamic oxaloacetic transaminase from 28 to 86 units/ml., cephalin flocculation from 1+ to 3+, thymol turbidity from 2 to 6 units, and alkaline phosphatase from 2.8 to 5.4 Bessey-Lowry units. The patient did not become icteric and had no signs or symptoms referable to the liver. The drug was discontinued, and within 1 month the abnormalities had disappeared. She was subsequently restarted on JB-516, without recurrence of the abnormal laboratory findings. There were no significant abnormalities detected by laboratory tests in other patients, except for occasional mild increases in the blood urea nitrogen during periods of marked hypotension.

Of the hospitalized group, Patient No. 4, a 39-year-old white woman, expired suddenly on the twenty-first day of therapy with JB-516. The patient had a prior history of syncopal episodes occurring about once a week, and had been hospitalized because of a myocardial infarction 6 months prior to death. The blood pressure remained unchanged in the range of 180/110 mm. Hg until the patient expired. The mode of exitus was that of sudden ventricular fibrillation following several hours of mild epigastric discomfort. Open-chest resuscitation was unsuccessful. At autopsy examination there was a considerable area of fibrosis of the posterior myocardium. Additionally, there was a large area of hyperemia in the anterolateral wall of the left ventricle. Marked arteriosclerotic changes of all major vessels were noted, particularly in the coronary and cerebral vasculature. The cause of death in this patient was attributed to myocardial ischemia with resultant disturbance in cardiac rhythm.

Inhibition of Monoamine Oxidase.—Chemical studies to demonstrate inhibition of MAO were carried out in 6 of the hospitalized patients. Fig. 6 illustrates the effect of JB-516 in diminishing the percentage of the daily oral dose (20 mg.) of serotonin converted to its MAO metabolite, 5-hydroxyindoleacetic acid. The

coincident decrease in standing blood pressure is also shown. A similar correlation of biochemical and physiologic effects was noted in 4 of the 6 patients in whom chemical data were obtained. However, the same degree and onset of inhibition of MAO were observed in both Patient No. 7, whose blood pressure did not respond until the fourteenth day of therapy, and in Patient No. 4, who had no blood pressure response even after 21 days of therapy. A comparison of the MAO-inhibiting action of JB-516 with that of other drugs is presented elsewhere.[7] The potency of JB-516 in this regard has been confirmed recently in this laboratory by the observation that a daily dose of 25 mg. produces a sixfold to tenfold rise in the urinary excretion of tryptamine.[8,9]

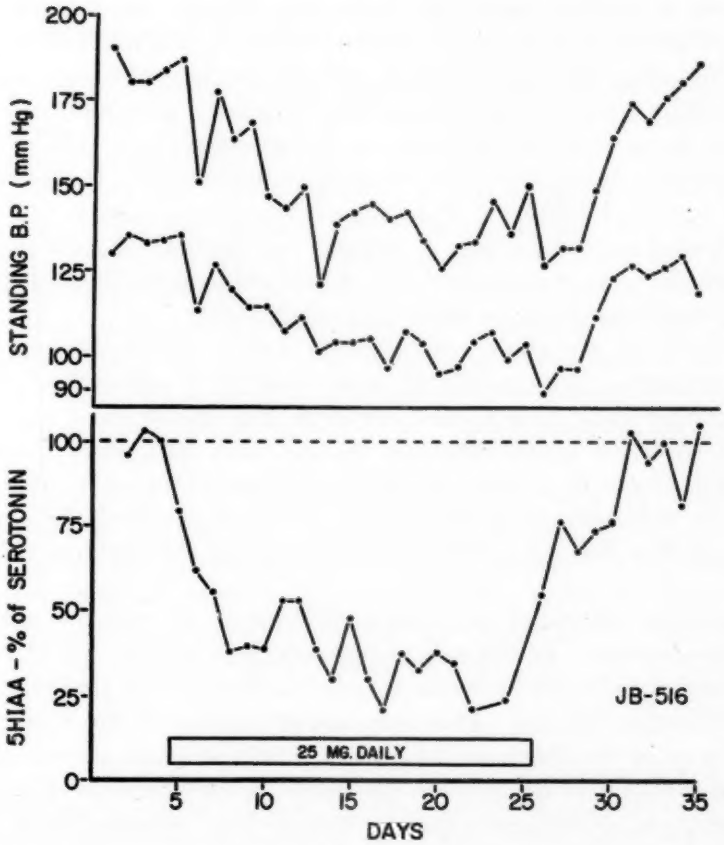

Fig. 6.—Effect of JB-516 on standing blood pressure and monoamine oxidase (measured by the decreased conversion of serotonin to 5-HIAA) in Patient No. 1.

DISCUSSION

This preliminary evaluation of JB-516 suggests that a sustained lowering of the standing blood pressure, and in some cases the recumbent pressure as well, can be achieved with this agent in a high percentage of patients with hypertension. The effects of JB-516 mimic those produced by sympathectomy and ganglionic blocking agents, but do not appear to be associated with the parasympath-

olytic effects commonly seen with the latter group of drugs. The drug has the additional advantage of producing a sustained postural effect even though only a single daily dose is administered.

It appears that the optimal maintenance dose in hypertension ranges from 6.25 to 12.5 mg. daily. When therapy is initiated, particularly if a relatively rapid effect is desired, the dose schedule should begin at from 25 to 50 mg. per day under close observation, and the dosage decreased when a hypotensive effect becomes manifest. Since JB-516 is a long-acting drug, it is possible that maintenance therapy could be continued with even less frequent administration of the drug. This has not been attempted since it is easier for a patient to adhere to a daily schedule. Many patients will undoubtedly require the addition of chlorothiazide or another agent for long-term control. As has been noted, the addition of chlorothiazide seems to potentiate the hypotensive effects of JB-516, and it appears that this combination without further additions may suffice as adequate therapy for hypertensive patients covering a wide spectrum of severity. Recently, we have added hydralazine to the combination of JB-516 and chlorothiazide, without adverse effects in a few cases not included in this report. Sudden withdrawal of JB-516, as was done in the patients with the color defect, may be undesirable. In 2 of the 6 patients developing the color defect, marked rises in the blood pressure occurred, and 3 of these patients developed mild symptoms of psychic depression for short periods of time.

Impairment of red-green color discrimination is a most unusual effect of a therapeutic agent. To consider an optic neuritis or some other toxic event as the cause of this color defect does not seem reasonable since no other abnormalities on standard ophthalmologic testing were observed. Since immediate cessation of the administration of JB-516 was considered advisable prior to establishing the reversibility of this defect, we have not had the opportunity to investigate further this color defect and its possible relationship to inhibition of MAO.

The drug has thus far not been administered to patients with malignant or renal hypertension. In the oral doses employed to date, JB-516 does not act with sufficient rapidity to be useful in situations in which lowering of the blood pressure is an urgent matter. However, administration of much larger oral doses or employment of the parenteral route of administration are worthy of study. Another cardiovascular disorder to be tested with this new therapeutic agent is angina pectoris, since iproniazid has already been reported to have a decided antianginal effect.

The mechanism by which this drug produces orthostatic hypotension is unknown. The absence of compensatory tachycardia suggests that it is a sympathetic blocking agent rather than a noradrenergic blocking agent such as phentolamine (Regitine). It may be difficult to elucidate antihypertensive mechanisms in the dog, since the administration of large doses intravenously in this species produces a pressor response.[10] The pressor response in dogs may be due to the fact that JB-516 is the hydrazine analogue of amphetamine. Other MAO inhibitors have not been found to have this effect in the dog. The effects of the intravenous administration of JB-516 to human beings are not yet known.

The fascinating and difficult question which arises is whether a cause-and-effect relationship exists between amine-oxidase inhibition and the orthostatic lowering of the blood pressure. Studies in this laboratory attempting to answer this question have been presented elsewhere and are as yet inconclusive.[7] More biochemical studies should be done in cases such as that of Patient No. 4, in whom adequate inhibition of MAO without a blood pressure effect was observed. Also, further study is required using MAO inhibitors of differing chemical structure, in an attempt to correlate physiologic and biochemical responses in human subjects. It is already apparent that this approach may lead to the discovery of other useful therapeutic agents in hypertension, and also may lead to a better understanding of the biochemical mediation of hypertension.

SUMMARY AND CONCLUSIONS

A preliminary evaluation of the monoamine-oxidase inhibitor, 1-phenyl-2-hydrazinopropane (JB-516, Catron), in the treatment of hypertension indicates that the drug is a potent orthostatic hypotensive agent. An orthostatic lowering of the blood pressure was produced in 18 of 21 hypertensive patients. Six subjects also had a distinct lowering of the recumbent blood pressure. The lack of parasympatholytic effects in this study suggests that JB-516 or other drugs with this type of action may offer considerable advantage over ganglionic blocking agents in long-term management of severe hypertension. Six patients developed a loss of red-green color discrimination, without other visual defects, while receiving large doses of JB-516. Although this condition subsided promptly on discontinuance of the drug, it could impose limitations upon its use as a therapeutic agent in hypertension.

It is our impression that chlorothiazide potentiated the antihypertensive effect of JB-516 in several patients. Experience may show that this combination is more effective in many cases of hypertension than either drug alone.

Evidence of inhibition of monoamine oxidase by JB-516 in man is presented. Attention is directed to a possible relationship between the inhibition of this enzyme and the reduction of blood pressure.

ADDENDUM

Since this paper was submitted for publication, Patients E. H. and S. Y. (see Table II) have had a recurrence of the color defect while on therapy with JB-516 (12.5 mg. per day). Both patients also have been receiving chlorothiazide (1,000 mg. per day) and hydralazine (100 mg. per day), the latter drug having been added to the regimen three months ago. In both of these patients there has been a concomitant diminution of visual acuity. While Patient E. H. also has extensive hypertensive retinopathy (Grade III-IV), the funduscopic changes in S. Y. are only Grade II.

The incidence, degree, and types of effects on vision require further evaluation. Furthermore, the reversibility of the most recent alterations remains to be determined.

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The Clinical Evolution of Shunt-Operations for Morbus Caeruleus: Results of 150 Operations, in a Long-Term Follow-Up

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INTRODUCTION

The classical operations of Blalock,[4] Potts,[25] and Brock[6] which have been used for more than 10 years in treating the tetralogy of Fallot are purely symptomatic. Their aim is to augment the pulmonary circulation in order to increase the oxygenation of the blood. However, they do not, properly speaking, correct the malformation. In fact, with the procedures of Blalock and Potts a fifth malformation is created in a heart that already has four. It is well known that an operation which creates an artificial ductus arteriosus must, in the long run, produce a significant overloading of the heart. In any event, the immediate benefits of the operation, in so far as the general status of the patients and the amelioration of the cyanosis are concerned, are so evident that the undeniable usefulness of this type of operation is universally recognized.

TABLE I

AUTHOR AND YEAR	NUMBER OF PATIENTS	PROCEDURE USED (IN ORDER OF FREQUENCY)	OVER-ALL MORTALITY (PER CENT)	GOOD RESULTS (PER CENT)	FOLLOW-UP
Potts, 1956	514	Potts	9	?	?
Johnson, 1951	144	Blalock, Potts	12	?	?
Bret, 1952	172	Potts, Blalock, Brock	20	74	?
Derra, 1952	242	Blalock, Brock	19	76	?
Dubost, 1954	333	Blalock, Potts, Brock	16	78	?
Brock, 1955	140	Brock	11.5	76	?
Sellors, 1950	93	Blalock, Potts, Brock	10.5	68.5	6 mo. and more
Campbell, 1953	200	Blalock, Brock, Potts	16.5	68	From 1 to 4 yr.
Taussig, 1952	1,000	Blalock	15.7	77.3	From 18 mo. to 7 yr.
Potts, 1956	100	Potts	14	84	From 6 to 8 yr.

From the Department of Cardiology and Cardiac Surgery, St. Antonius Hospital, Utrecht, Netherlands. (The operations were performed by Prof. A. G. Brom and Dr. A. Schaepkens van Riempst. The anesthesiologist was Dr. H. De Zwaan.)

Received for publication Feb. 17, 1959.

But, what is the future of these patients? Since, thanks to the heart-lung apparatus (Lillehei[20]), we may now foresee the possibilities of plastic repairs within the heart of patients with tetralogy of Fallot, it seems necessary to analyze the long-term results of the palliative operations that we have used until now. There have been very few such studies in the literature up to the present time. Among the principal articles pertaining to this subject, we found only four which mentioned the evolution of the patients 6 months or more after the operation.[8,24,27,29] For the sake of comparison, Table I shows the over-all results of the most important studies that have been published.[5,8,10,11,13,15,23,24,27,29]

MATERIAL AND RESULTS

The material presented in this article was drawn from 141 cases, beginning with our first surgical intervention in 1948, and including those cases up to and through 1956. One patient emigrated to Canada, after being seen twice during the 10 months following his operation, and 2 died, 8 months and 6 years, respectively, after their operations, without having returned for checkups before death. All the others were examined on convocation in 1956 or 1957. Three fourths of them were regularly controlled every first or second year. The object of these examinations was to obtain precise information in order to learn: (1) whether avoidable errors in the evaluation of the operability of our patients were committed; (2) whether it was possible to establish for each case the optimal size of the shunt to be made; (3) whether there were reasons to prefer one of the procedures used (Blalock, Potts, or Brock) to the others; and (4) whether these operations still benefited the patients years afterward.

The results were based primarily upon the ensemble of the clinical symptomatology. The results were called *excellent* in those patients whose physical capabilities were in no way limited after surgery; they were called *good* in those patients whose condition showed a marked improvement, allowing them to lead normal lives for their ages, with the exception of violent or prolonged physical efforts. The results were considered as *insufficient* in those patients in whom there was no appreciable change seen after surgery. Finally, *mortality*, whether precocious or tardive, and no matter of what origin, constituted the fourth category.

Fig. 1 shows the over-all results of our cases and provides the key to our schemata, wherein the failures (deaths and insufficient results) are always compared in per cent to the successes (excellent and good results). Fig. 1 is interpreted as follows: deaths: 33 cases, or 23.5 per cent; insufficient results: 5 cases, or 3.5 per cent; good results: 81 cases, or 57.5 per cent; excellent results: 22 cases, or 15.5 per cent.

Besides those total results, we have attentively analyzed several factors which may influence favorably or unfavorably the postoperative evolution of our patients. These factors are discussed below.

FACTORS INFLUENCING PROGNOSIS

Diagnosis.—Patients with different types of congenital cyanosis were operated upon, including 10 who had tricuspid atresia or stenosis with atrial and ventricular septal defects, without operative death. It is possible to obtain very good results in these cases, even after 6 years or more. The results may be very spectacular, as in the case of the 13-year-old boy suffering from pulmonary tuberculosis with cavitation, who, after a Potts operation, recovered rapidly in a sanatorium, and who, at the age of 17-½ years, could work and lead a normal life.

Six patients presented a rare malformation such as tetralogy of Fallot with a large monoatrium (2 cases) or complicated by an atrioventricularis communis

(1 case), a pseudotruncus arteriosus, a valvular and infundibular pulmonary stenosis with cor biloculare, a transposition of the great vessels with pulmonary stenosis and monoventricle. There were 5 operative deaths in this series. The indication for surgical intervention in each of these cases was the right-to-left ventricular shunt and the insufficiency of the outflow of the pulmonary artery.

Eleven patients had no precise preoperative diagnosis. All seemed to fall within the framework of the tetralogy of Fallot, while presenting such atypical manifestations as an enlarged heart due to a large interauricular septal defect, a monoventricular form, or an excessively overriding aorta. Here too, there were 5 operative deaths.

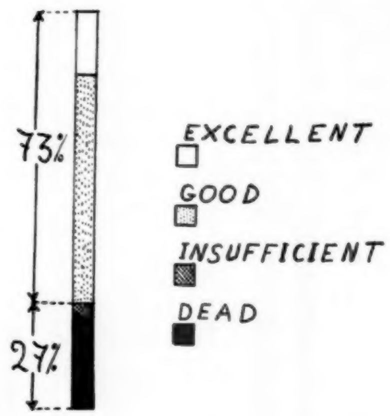

Fig. 1.

One patient with a transposition of the great vessels, who was not catheterized, underwent only a useless explorative thoracotomy.

Excluded from our study were the cases of pulmonary stenosis with intact ventricular septum (trilogy of Fallot), in which shunt-operations were contraindicated.

Finally, there were 113 typical examples of the tetralogy of Fallot. Fig. 2 shows that the results were much better in patients with the tetralogy of Fallot (right side) than in those with the rarer forms of cyanotic heart disease (left side).

We also noted, as have others,[14,18] that the absence of a whisper is a bad prognostic sign. This generally indicates a serious malformation accompanied by pulmonary atresia or extreme pulmonary hypoplasia. We did not hear at all the usual systolic whisper in the patient with pseudotruncus arteriosus mentioned above, nor in another patient, 27 years old, in whom we could reach the aorta but not the pulmonary artery by catheterization, although he presented all the clinical, radiologic, and electrocardiographic features of a classic tetralogy of Fallot. Both patients died during the operation.

The importance of a preoperative diagnosis as exact as possible is still to be pointed out. For that reason, a catheterization or angiocardiographic study, or both, has been systematically carried out in all of our patients, without any important accident. In all, 130 angiocardiographic studies and 139 catheteriza-

tions were made. An overriding aorta was evident in 73 of the angiocardiograms. Typical angiocardiograms were obtained in our 10 cases of tricuspid atresia or stenosis with auricular and ventricular septal defects. However, generally, the information obtained by angiocardiography was not so precise as that obtained by catheterization. Angiocardiography is only indicated in children less than 1 year old, and when the desired information cannot be obtained by catheterization. It was in these cases that selective angiocardiography by intracardiac injection gave the most precise data. The two great vessels were sounded in 58 patients by catheterization, the pulmonary artery only in 7 cases, and the aorta only in 3 cases.

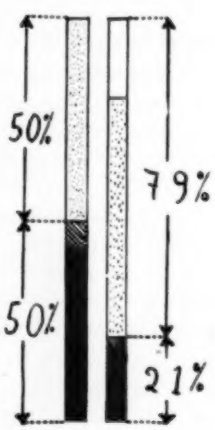

Fig. 2.

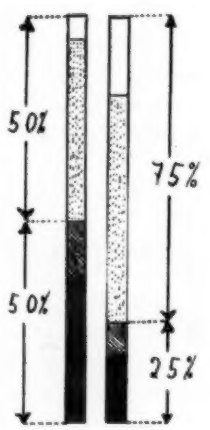

Fig. 3.

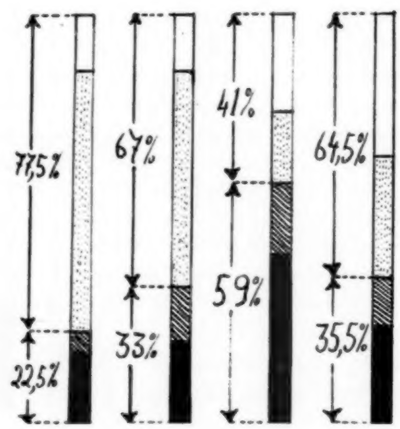

Fig. 4.

In our 141 patients we were able to get 123 exact diagnoses, and only an indication for surgical procedure in 17 instances, in cases of insufficiency of the outflow of the pulmonary artery and right-to-left ventricular shunt. We had only one erroneous diagnosis (a transposition of the great vessels) in an 8-month-old child, resulting in a useless thoracotomy. Taussig,[29] who referred to a time when catheterization was not done systematically, described 40 grossly erroneous diagnoses resulting in 33 operative deaths in her series of 1,000 cases.

Age at Time of Operation.—The patient's age at the time of operation was also an important factor. The younger the children the greater are the risks of failure. The risks are also greater in adults than in adolescents. The left-hand column of Fig. 3 represents the 38 operations performed on patients who were less than 2.5 years or more than 17 years old, and the right-hand column represents the 112 operations performed on patients between these two ages. Similarly, we noticed that the sooner the clinical manifestations appeared, the worse were the results.

Type of Operative Procedures.—In 9 of the 141 cases a second operation was performed because of insufficient results obtained from the first operation. The distribution of the 150 operations performed was as follows: 88 Potts, 42 Blalock, and 17 Brock procedures, 1 explorative thoracotomy, and 2 deaths under narcosis before surgery was begun. Fig. 4 illustrates, from left to the right, the results obtained with the Potts, Blalock, and Brock methods; the last column on

the right represents the 17 very first operations we did (only Potts or Blalock methods used). That last comparison has convinced us that, in spite of some excellent results, the operative mortality was clearly greater with the Brock procedure than with the two other procedures. Six of the patients surviving after the Brock procedure were recatheterized within 7 months and 5 years postoperatively. All showed the persistence of a considerable gradient between the systolic pressure in the pulmonary artery and that in the right ventricle (from 65 to 105 mm. Hg). These considerations led us, as well as others,[3,9,15,28] to use exclusively the usual shunt-operations, and to abandon the Brock procedure.

Nine other catheterizations (6 using the Potts procedure and 3 using the Blalock procedure) were performed from 8 months to 6 years postoperatively. The pressure in the right ventricle was always in equilibrium with the pressure in the aorta, between 95 and 120 mm. Hg. The oxygen saturation of the arterial blood was always higher than before the operation. A right-to-left shunt was already predominant preoperatively, while after the operation the shunt was left-to-right. Little importance was attached to the quantitative evaluation of the outflow of the shunts, because we found this calculation to be too easily subject to great error.

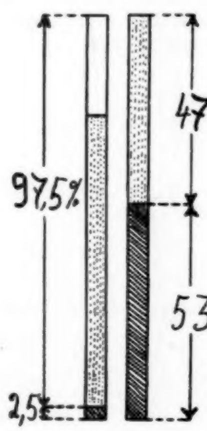

Fig. 5.

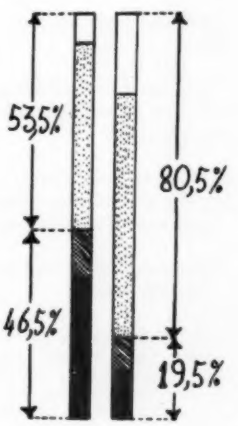

Fig. 6.

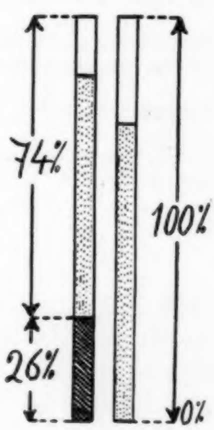

Fig. 7.

Causes of Death.[2,8,11,19,24,27,29,31]—Table II lists the causes of death, which have been divided into three groups. It is to be noted that 4 fatal ventricular fibrillations took place during the Brock operation, which number represents a large proportion.

On the other hand, 3 of the patients who died from asystole had obtained too large a shunt (more than 6 mm. in diameter) with the Potts procedure. But postoperative results were frequently insufficient when a small shunt (less than 4 mm. in diameter) was created by operation (Blalock or Potts procedure). The most adequate shunts were always found between the values of 4 and 6 mm. in diameter. Of all the patients who underwent the Potts or Blalock procedure, the systolodiastolic whisper of the artificial shunt was absent in only 2 cases (children who died from postoperative complications). It is probable that the occlusion of the shunt played a major role in the fatal evolution in these cases.

Finally, it is to be noted that only 1 case of sepsis caused a late death; this was a very small number in view of the reputation that shunt-operations have of favoring the appearance of such an infection.

TABLE II. CAUSES OF DEATH

IMMEDIATE OPERATIVE DEATHS (DURING THE FIRST HOURS OR DAYS AFTER THE OPERATION)	DEATHS DUE TO POSTOPERATIVE COMPLICATIONS (FROM THE FIRST WEEK TO 6 MONTHS AFTER THE OPERATION)	LATE DEATHS (FROM 8 MONTHS TO 6 YEARS AFTER THE OPERATION)
(18 cases= 13%)	(11 cases= 8%)	(4 cases= 3%)
1. Cardiac arrest in preoperative narcosis (2)	1. High fever of unknown origin, 3 days postop. (1)	1. Accidental death by car, 8 months postop. (1)
2. Cardiac arrest during surgical procedure (4)	2. Capillary bronchiolitis, 1 week postop. (1)	2. Progressive cardiac failure by too large a shunt, 3 years postop. (1)
3. Hemorrhage from a bad joining in the first hours (2)	3. Hemopyopneumothorax, 1 week postop. (1)	3. Death 3½ years after a Blalock operation, complicated by a severe right hemiplegia, by too small a shunt (1)
4. Pulmonary edema during operation resulting in cardiac arrest in the following hours (2)	4. Severe bronchopneumonia, 3 weeks postop. (1)	4. Sepsis (hemolytic streptococcus) 6 years postop. (1)
5. Cerebral anoxia with death in the first 36 hours postop. (2)	5. Infectious hepatitis, 2 months postop. (1)	
6. Postoperative shock (1)	6. Death after 3 months from purulent pleuritis (*Staphylococcus aureus*) (1)	
7. Cardiac arrest in the first 48 hours postop. (5)	7. Thromboembolic disease resulting in fatal mesenteric thrombosis after 4 months (1)	
	8. Encephalitis with fatal issue, 5 months postop. (1)	
	9. Cardiac failure, by too large a shunt, 2 to 6 months postop. (3)	

Weight.[26]—The mortality was about twice as frequent in puny children who were underweight than in those whose weight remained within the normal values. In the postoperative evolution more than one year after the operation, we noted insufficient results four times less often in children whose weight was normal than in those remaining underweight.

Condition of the Blood.—Examination of the blood also gave a clear indication of the prognosis. There were twice as many deaths in 6 patients suffering from anemia (less than 80 per cent hemoglobin) than in the 22 patients having a particularly important cyanosis (more than 140 per cent hemoglobin). After operation, the hemoglobin level in 19 patients remained high as compared with the others in whom it was obviously lower or remained within normal limits. Fig. 5 shows the strikingly different results between the 19 unfavorable evolutions of the blood condition (right-hand column) and all the others (left-hand column).

Size of the Heart on X-Rays.[7,8,11,19,22,24,30,31]—Before operation, among all the patients submitted to surgery for congenital cyanosis, independent of the

exact diagnosis, it was striking to ascertain how much better was the prognosis of the patients whose heart was normal or small in size than was the prognosis of those with enlarged heart. The left-hand column of Fig. 6 shows the 41 cases in which the cardiothoracic ratio was higher than 52 per cent, and the right-hand column shows the others, in which it was lower than 52 per cent. On the contrary, after operation, the cases with unfavorable results were those 27 in which the heart did not become larger, probably because of the failure of an adequate shunt (Fig. 7, left-hand column); in the others the cardiothoracic ratio increased from 2 to 6 per cent, and the results were better (Fig. 7, right-hand column). Similarly, the x-ray pictures in the cases with good results show generally well the darker outline of the pulmonary vessels, which reflects the efficacy and utility of the shunt.

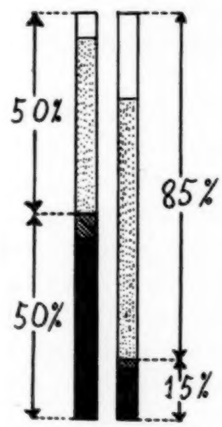

Fig. 8.

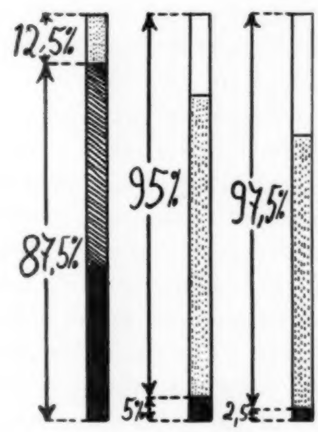

Fig. 9.

Electrocardiographic Features.[1,11,12,16,19,21,22,24,32]—The following electrocardiographic features have been pointed out before surgical procedure: (1) Left axis deviation between $+20°$ and $-90°$ or signs of hypertrophy of the left ventricle on the precordial leads, or both, were observed in 4 cases of the rare forms of cyanotic heart disease and in the 10 cases of underdeveloped right ventricle. We counted here neither the cases with doubtful left axis deviation without hypertrophy of the left ventricle nor the cases with left axis deviation due to situs inversus or other unusual rotations of the heart. (2) Extreme hypertrophy of the right ventricle was judged to exist if two of the following data were present: R_{V1} greater than 20 mm. or $R_{V1} + S_{V6}$ greater than 35 mm.; intrinsicoid deflection larger than 0.06 second in V_1; P higher than 5 mm. in the right precordial leads; extreme right axis deviation of more than $+160°$. These findings were seen in 10 of the cases of rare cyanotic heart disease, and in 24 of the cases of tetralogy of Fallot. (3) A third group of cases did not show any of the aforementioned features. Fig. 8 shows, in the left-hand column, the 48 bad cases of the first and second group in comparison, in the right-hand column, with the 89 others of the third group.

After operation, it was possible to distinguish three different electrocardiographic evolutions; they are represented from left to right in Fig. 9: (1) Of the

8 patients in whom clear signs of progressive right overloading appeared, 3 died, 4 had unsatisfactory results, and only 1 had good postoperative results. It is obvious that this type of evolution had a very unfavorable prognosis. (2) In 40 patients there was no appreciable modification of the electrocardiogram. (3) In 43 patients there was a clearly observable increase in the potentials of the left ventricle. It was this latter group which had the most favorable evolution.

It is important to point out that the radiologic increase in the size of the heart as well as the electrical increase in the potentials of the left heart reflect the overwork of the left heart, resulting from the creation of the operative shunt. Those two modifications indicate that the shunt works usefully. At first progressive, the signs usually stabilize after 1 or 2 years in each patient when a satisfactory hemodynamic equilibrium has been reached. It is only in the rare cases of progressive asystole that we have not observed stabilization of the signs of increasing work of the left heart.

Test of the Function of the Heart.—The test of the function of the heart, described elsewhere by Jongbloed, van Nieuwenhuizen and van Goor,[17] consists in a continuous recording of the oxygen consumption of a patient at rest and during moderate effort (pedaling a cycle with a known resistance). The graphic curves thus recorded permit the calculation of the oxygen debt due to the effort. The oxygen debt is considered to be normal when it is less than 16 per cent of the increase in oxygen consumption due to a standard effort of 60 watts during a period of 8 minutes. The time necessary for a return to basal conditions normally should not exceed 3 minutes. Extracardiac factors have little influence on the results of this test, and these results are considered an excellent reflection of the functional capacity of the heart. Unfortunately, only well-developed adolescents, who are at least 15 years old, can use the cycle which has been standardized for adults.

Before operation, the results of this test were always poor. A third of the patients who had excellent clinical results when examined postoperatively had a normal or almost normal test of cardiac function. The results of the test were fair in patients with good clinical results, and poor in 2 cases with poor clinical outcome. Fig. 10 illustrates the evolution of the results of the test of cardiac function in a 19-year-old boy. The top graph shows the results of the test before the operation. The patient was unable to exert effort for longer than 2 minutes and 40 seconds. The oxygen debt (striped part of graph) is large and lasts for 5 minutes and 30 seconds. The theoretical steady state (the horizontal line on top) has not been reached. This graph shows a very poor cardiac function. The middle graph shows the results of the test 3 months after a Potts operation. The patient is able to put forth effort for a longer time. The curve reaches the steady state. The oxygen debt is still large and lasts for 5 minutes and 5 seconds. This graph shows a mediocre cardiac function. The bottom graph shows the results of the test 20 months after the operation. The standard effort of 8 minutes can be made. The steady state has been reached, and the oxygen debt is 21 per cent and lasts for 3 minutes and 10 seconds. Even though this shows a good cardiac function, it is still not normal. Fig. 11 shows a test of the function

of the heart that was within normal limits 5 years postoperatively. The oxygen debt is 15 per cent, and lasts for 2 minutes and 50 seconds; the standard effort is made easily and the steady state is reached quickly.

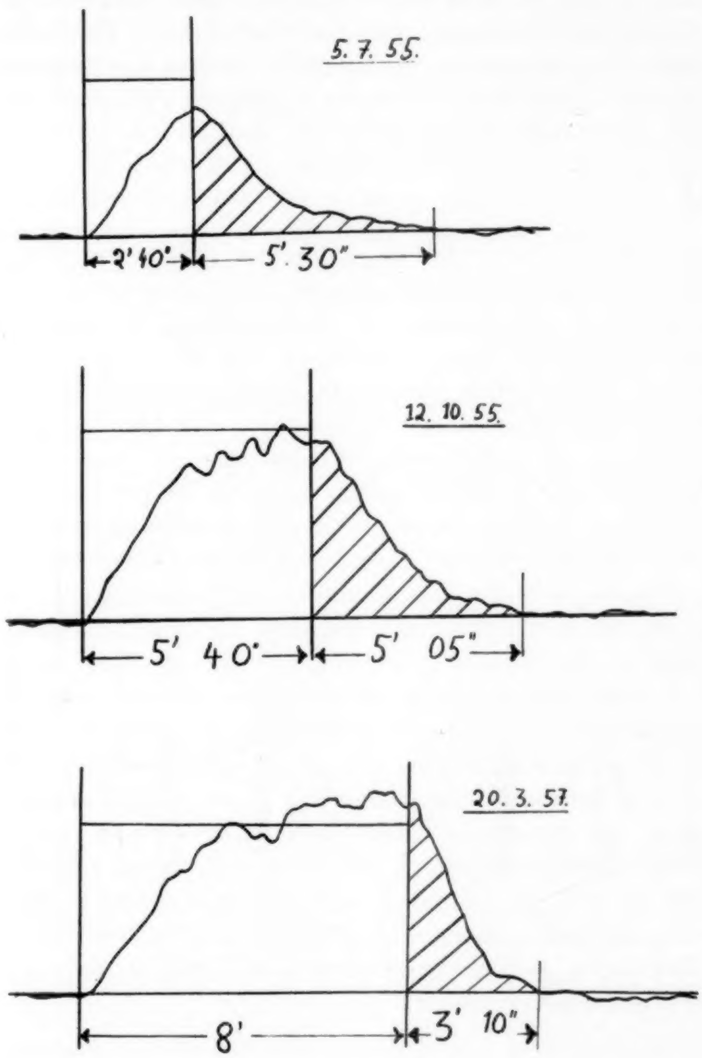

Fig. 10.

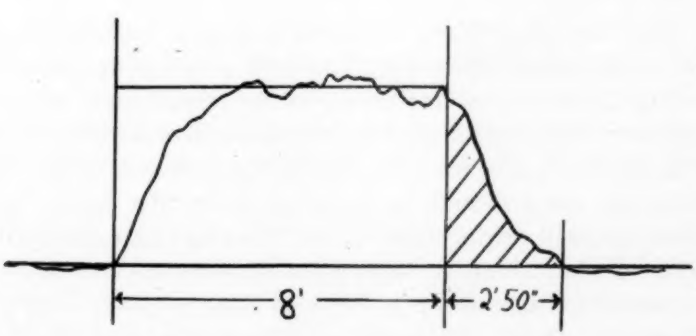

Fig. 11.

It is not surprising that the results of the test were below normal in patients who were considered clinically as having had good postoperative evolution, since the maximum that may be hoped for in these cases is an improvement of the hemodynamic conditions sufficient to permit a good adaptation. However, in 10 patients, results within normal limits were obtained. This is quite remarkable, because often the advances in the results of the test are progressive in character, and because our experience with the cardiac function test (in more than 1,000 cases) shows that it is very sensitive.

PROGNOSIS

As has been shown, there are many factors that seem to aggravate the prognosis. The following are the most important of these factors that adversely influenced the prognosis: (1) *Diagnosis:* cases in which the malformation found did not correspond to those found in a classic case of tetralogy of Fallot. (2) *Electrocardiogram:* cases which presented electrocardiographic features of a left or an extreme right ventricular hypertrophy. (3) *Age:* cases in which the patients were younger then 2.5 years or older than 17 years. (4) *Radiology:* cases in which there was a cardiothoracic ratio of 55 per cent or more. (5) *Hemoglobin:* cases in which the hemoglobin was more than 150 per cent or less than 70 per cent. (6) *Development:* cases in which the patients were underweight by more than 10 per cent of the normal values. (7) *Precociousness of symptoms:* cases in which the signs of circulatory disturbances were accentuated at birth.

On the basis of the foregoing criteria, we have divided our patients into three groups: I. *Cases with a good prognosis:* those patients who before surgical intervention had none of the seven factors listed above (49 cases, left-hand column of Fig. 12). II. *Cases with an average prognosis:* those patients who before surgery had only one of the factors listed above (52 cases, middle column of Fig. 12). III. *Cases with a poor prognosis:* those patients who before surgery had from two to six of the factors listed above (49 cases, right-hand column of Fig. 12).

If Groups I and III are compared, it is seen that the mortality ranges from 4 to 41 per cent, and in the cases with excellent results, from 29 to 4 per cent. Those cases that had a good prognosis had a mortality of only 4 per cent and had very good postoperative results.

LATE EVOLUTION OF THE RESULTS OBTAINED

The results of our study have a certain stability, because they have been calculated after an extended follow-up. In effect, it is during the first postoperative years that the majority of the unfavorable results were recorded. However, after 2 years or more, we reached a remarkable stabilization of the amelioration obtained from the operation. In certain cases this amelioration was progressive in character, even though at times momentarily halted by special circumstances (rapid growth during puberty, or too large an expenditure of energy in children who were too active). We were astonished by the fact that the majority of our patients became better and not worse as time passed. This was probably due to the following factors: (1) better oxygenation of the arterial blood, and

then of the myocardium; (2) better filling and functioning of the left ventricle, producing a more adequate outflow; (3) creation of the shunt by low pulmonary arterial pressure, that enables it to be efficient.

In those patients who survive, the results tend to stabilize. This is demonstrated by the analyses of Taussig[29,30] and Potts,[24] and holds true in our study. Fig. 13 shows that the number of failures did not increase as the years passed. In Fig. 13, one sees from the left to the right: (left-hand column) 141 patients who were followed up within the first 2 years after the operation; (middle column) 97 patients who were followed up for the last time from 2 to 5 years postoperatively; and (right-hand column) 50 patients who were followed up for the last time within 5 and 8 years postoperatively. However, after many years (10 to 15 years and probably longer) the mortality rate may again rise because of cardiac insufficiency. To be sure, our patients never regained a normal heart, but rather, they developed acceptable circulatory conditions that ought to permit them to live to a respectable age: 40 or 50 years or even longer. The remarkably good results of the test of the function of the heart confirms the optimism of those prognostics.

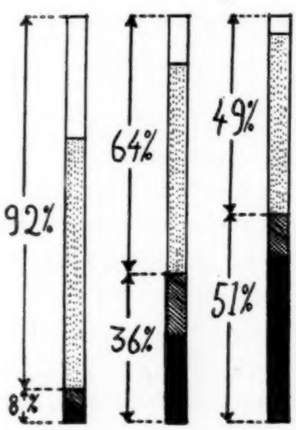

Fig. 12.

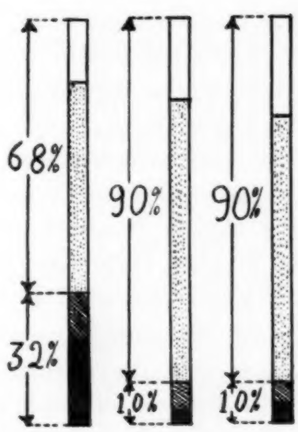

Fig. 13.

CONCLUSIONS

It is possible to establish criteria for making a good preoperative prognosis in cases of cyanotic malformations of the heart. The optimal size of the operative shunt to be made must range from 4 to 6 mm. in diameter. The best results are to be had with the Potts and Blalock procedures; the Brock operation should be avoided because of a high operative mortality, probably as a consequence of the frequency of the infundibular type of the stenosis in the tetralogy of Fallot. Finally, the shunt-operations still benefit the patients many years later.

The problem of treating congenital cyanosis still has not been resolved up to the present time. The prospects of surgical correction of these malformations with the aid of a heart-lung machine will enable us gradually to abandon the old methods of Blalock, Potts, and Brock. The aim of the surgeon always is

to try to reconstruct a normal anatomic situation. However, anatomic restoration does not necessarily correspond to normal physiologic function, nor to a good clinical state. The results of the newer methods have not been very encouraging in so far as congenital cyanotic disease is concerned. In 1957, Lillehei[20] presented a series of 60 cases of tetralogy of Fallot operated upon in this manner, in which the immediate operative mortality was 33.3 per cent. This mortality was quite high, in spite of the favorable choice of patients, who were always more than 3 years old, and who could not be too old, because of the small outflow that the artificial heart permitted at that time. When a stenosed pulmonary valve can be incised and a small interventricular communication can be sutured, it is certain that the result will be a heart that is practically normal, with maximal possibilities for the patient's survival; this result is certainly superior to that obtainable from the Potts operation. However, cases which are so favorable are rare, and until now, we know nothing about the long-term evolution of the patients who have survived such an operation. It is questionable whether the restoration of the outflow tract of the right ventricle would permit good hemodynamic function for many years. Also, sufficient information is not yet available to confirm whether the plastic material used in these operations will be perfectly well tolerated with the passing of time.

These objections are even more valid since the long-term results of the shunt-operations are even better than expected. The patients whose progress has been stabilized a year or two after the operation have acquired an astonishing physical capacity, sometimes even a normal physical capacity, as has been confirmed by the cardiac function test. This improvement is still present after a lapse of 6 to 8 years, with these patients showing neither a weakening of their general condition nor signs of the beginning of a cardiac failure.

The aim of this study was to bring up to date the information concerning shunt-operations and the postoperative evolution of patients undergoing such operations. In making our evaluation we have tried to find as precise criteria as possible in order to give a preoperative prognosis and to evaluate the results obtained. These criteria will permit us in the future to compare the new and the old methods. For the present we ought to be satisfied with the notable stability of our operative results, a stability which to a large extent conforms to the results of Taussig[30] and Potts.[24]

SUMMARY

This paper reports a study of the long-term results of 150 operations for congenital cyanosis in 141 patients. All living patients, except one, were re-examined in 1956 or 1957. A preoperative prognosis was made, taking various factors (age, hemoglobin content, electrocardiogram, roentgenogram, etc.) into account. In those cases having a favorable preoperative prognosis, 90 per cent had good postoperative results, one third of which were excellent, the mortality being 4 per cent. The mortality was 10 times higher in cases with unfavorable preoperative prognosis. The cases in which the Potts operation was used were the most successful. The successful postoperative results obtained from the

three operations used (Potts, Blalock, and Brock procedures) were seen to be durable during the years that followed. In general, the postoperative modifications in the clinical signs, the electrocardiograms, and the roentgenograms were stabilized within the first two years after the operation. Some patients, even after a period of several years, were considered to have normal cardiac function, according to their performance in a cardiac function test that is described in the text.

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Aplasia or Hypoplasia of One Pulmonary Artery: Radiologic and Pulmonary Function Studies

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INTRODUCTION

Physicians today are expected to be on the alert for anomalies and for diseases that only a few years ago were considered to be rare and/or exotic. Aplasia or hypoplasia of a pulmonary artery can no longer be classified in this category. Frantzel,[1] in 1868, first recorded the absence of a branch of the common pulmonary artery. Until 1952, only nine cases had been reported, all diagnosed at autopsy or surgery.[1-9] Since Madoff[10] first demonstrated the absence of the right pulmonary artery by angiocardiography, the diagnosis has been made much more frequently. Recent reports and our experience suggest that this anomaly is not rare. A review of the literature shows that the diagnosis has been made by angiocardiograms at least 20 times. Hypoplasia or absence of a pulmonary artery may occur alone or in association with other congenital abnormalities of the vascular system.[11] When either hypoplasia or absence of a pulmonary artery occurs alone, the diagnosis may be missed.

It is possible to make an accurate clinical diagnosis of hypoplasia or absence of a pulmonary artery. The purpose of this paper is to report on seven patients in whom such a diagnosis was suspected clinically and confirmed by angiocardiography and bronchography. Some of our case histories will illustrate the varied diagnoses as well as the unnecessary treatment offered to the patients. Pulmonary function studies have been reported by others[10-15] in ten patients with hypoplasia or absence of the pulmonary artery (Table I). Because of the small number of pulmonary function studies reported, we performed pulmonary function tests whenever possible in order to elucidate further the physiologic changes.

In general, our clinical findings in hypoplasia or absence of one pulmonary artery were similar to those reported by others. These findings include asymmetry of the thorax, diminished expansion and decreased breath sounds on the affected side, hyperresonance over the unaffected side, and sometimes a systolic murmur along the left sternal border or at the cardiac apex. Symptoms of cough, shortness of breath, hemoptysis, and recurrent pulmonary infection are common. Some patients are asymptomatic. Routine chest roentgenograms

Received for publication Jan. 30, 1959.

confirm the physical findings of thoracic asymmetry, high diaphragm, and decreased expansion on the affected side, and show a difference in the vascularity of the two lung fields, a most important diagnostic sign. Wyman[16] has reviewed and summarized the radiologic findings.

MATERIALS AND METHODS

Seven patients with hypoplasia or absence of one pulmonary artery were seen at the University Hospitals in Iowa City. Each patient had a complete physical examination and the indicated laboratory tests. Angiocardiograms were made after rapid injection of Diodrast into an antecubital vein. X-ray exposures were made at intervals of 0.5 to 1 second with a Sanchez Perez Seriograph. Pulmonary function tests were made in the morning after the patient had eaten breakfast. The vital capacity, inspiratory capacity, and expiratory reserve volume were measured separately by a Benedict Roth spirometer. The best of three trials was recorded. The functional residual capacity of the lungs was measured in duplicate by the nitrogen washout method of Darling, Cournand, and Richards.[17] Volumes were corrected to body temperature, and ambient pressure, and saturated with water vapor, hereafter called BTPS. Rate, depth, and minute volume of ventilation were measured while the patient was breathing air, 99.6 per cent oxygen, and 7.5 per cent carbon dioxide in air. Expired samples were collected in a Tissot spirometer simultaneously with the drawing of samples of arterial blood. Volumes were corrected to BTPS. Uniformity of intrapulmonary distribution of inspired gas was checked by the single breath nitrogen test of Comroe and Fowler.[18] The measurement of the percentage of nitrogen at the end of 7 minutes of breathing oxygen was made as described by Cournand, Baldwin, Darling, and Richards.[19] To measure maximal breathing capacity (MBC), the patient was directed to breathe for 15 seconds through a mouthpiece, low-resistance valve, and wide tubing into a Tissot spirometer. The highest value obtained in three trials was calculated in liters per minute. Maximal inspiratory (or expiratory) flow rate was measured between 200 and 1,200 ml. of the inspiration (or expiration) according to the method of Danzig and Comroe.[20]

Arterial blood was obtained from the brachial artery while the semirecumbent subject breathed air, and again after he had breathed 99.6 per cent oxygen for at least 10 minutes. Continuous analysis of CO_2 in expired alveolar gas was made by the CO_2 analyzer during the drawing of arterial blood. The arterial samples were analyzed for total oxygen content, oxygen capacity, and carbon-dioxide content of whole blood by the manometric technique of Van Slyke and Neill.[21] Blood was rotated in a tonometer with air at room temperature for 20 minutes before measuring oxygen capacity. Appropriate corrections were made for physically disolved oxygen and for differences in total hemoglobin in the content and capacity samples. Dissolved oxygen was not measured directly, but an approximate calculation was made on the samples collected during the inhalation of oxygen by subtracting the oxygen capacity from the total oxygen content. Arterial blood pH was measured in a closed Cambridge glass electrode at 37° C., unless the measurement was made at room temperature, in which case the pH value was corrected to 37° C., using the factor of Rosenthal.[22] Plasma carbon-dioxide content and P_{CO_2} were determined from pH, oxygen capacity, and whole blood carbon-dioxide content by use of the monogram of Singer and Hastings.[23] Diffusion was studied using the single breath carbon-monoxide method of Ogilvie, Forster, Blakemore and Morton.[24]

CASE REPORTS

CASE 1.—C. F., an 18-month-old girl, was admitted to University Hospitals 3 days after an acute respiratory episode. The parents stated that the patient had been well until 3 days before admission, when a sister had stepped on the patient's finger. The patient gasped, became cyanotic, and stopped breathing. An aunt applied artificial respiration for a few minutes, and then normal breathing resumed. Subsequently, the child had no complaints except for fatigue and a slight cough. She was afebrile. The attending physician's initial impression was atelectasis of the left lung, possibly due to inhalation of a foreign body.

Abnormal physical signs were limited to the chest. The left side was decreased in size and in expansion. It was dull to percussion. There were diminished breath sounds. The right side was hyperresonant and the breath sounds were normal. The heart was shifted to the left. A Grade 3 harsh systolic murmur was heard along the left sternal border, loudest in the pulmonic area. The pulmonic second sound was loud and split.

The hemoglobin was 14 Gm., and the white blood cell count was 6,500 with a normal differential. The urinalysis was normal.

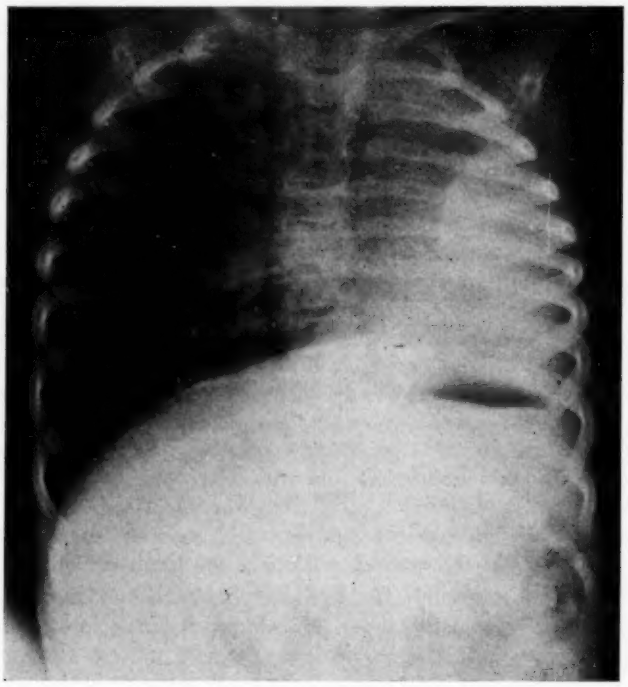

Fig. 1.—Case 1. Posteroanterior film of the chest showing total absence of the left pulmonary artery. No pulmonary arteries can be seen on the left. On the right they are well visualized, especially in the base.

The chest x-ray is shown in Fig. 1. It demonstrates displacement of the heart to the left, compensatory emphysema of the right lung, and herniation of a portion of the right lung into the left hemithorax. The trachea is in the midline. No pulmonary vessels are seen on the left. Large pulmonary arteries are seen on the right, particularly at the base. The initial interpretation was complete atelectasis of the left lung. A foreign body was suspected. Bronchoscopy revealed no evidence of a foreign body or other abnormality. The bronchogram was interpreted as showing an anomalous left lower lobe surrounded by diminutive alveoli but without upper lobe or lingula. An alternate explanation was that there was no left lung, and that the right lower lobe was anomalous—coming off the main stem vertically as a single trunk with the middle lobe in the space normally occupied by the lower lobe. The upper lobe bronchus was incompletely filled. To clarify the situation, angiocardiograms were made (Fig. 2). Cardiac rotation, absence of the left pulmonary artery, and the compensatory dilatation of the right main pulmonary artery and its branches are seen. The pulmonary artery going to the anomalous lower lobe can be seen. This lower lobe, therefore, arises from the right trunk rather than the left. A later film clearly revealed the large tortuous and displaced right pulmonary veins and the displaced aorta.

At exploratory thoracotomy, agenesis of the left lung and complete atresia of the left pulmonary artery were found. The postoperative course was satisfactory.

CASE 2.—O. H., a 50-year-old white carpenter, was admitted to University Hospitals with the chief complaint of a chest cold for 3 months. He had been in good health until he developed shortness of breath and cough. He had lost about 30 pounds. Past history revealed two episodes of pneumonia. His family physician thought that he had carcinoma of the lung.

The abnormal physical findings were limited to the chest. The right hemithorax was smaller and narrower than the left. Dullness was present and breath sounds were decreased over the right lung anteriorly and posteriorly. The heart was shifted to the right. There were no cardiac murmurs.

The hemoglobin was 16 Gm., the red blood cell count was 5.28 million, and the white blood cell count was 7,600. The urinalysis was normal. No bacteria or abnormal cells were found in the sputum. The electrocardiogram showed residual changes of a high anterolateral myocardial infarction.

Fig. 2.—Case 1. Angiocardiogram taken at 1.5 seconds, demonstrating total absence of the left pulmonary artery. Note the curving branch leading to the anomalous lower lobe.

A roentgenogram of the chest (Fig. 3) demonstrated a diminutive right hemithorax, with slight rotary shift of the heart and mediastinum to the right, a lobulated elevation of the lateral portion of the right leaf of the diaphragm, and a distorted and diminished vascular pattern. The left pulmonary artery was increased in size and density. Bronchograms demonstrated an abnormal take-off of the right main bronchus and its first two divisions. The distribution of these divisions was abnormal and the alveoli were sparsely filled.

The angiocardiogram is seen in Fig. 4. The left pulmonary artery is twice the size of the right. There is irregular distribution and distortion of the right pulmonary artery.

The final diagnosis was hypoplasia of the right pulmonary artery and bronchitis. The patient's symptoms improved with postural drainage and bed rest, and he was discharged.

CASE 3.—J. P., a 44-year-old housewife, was admitted to University Hospitals because of pain and weakness of the left leg. A diagnosis of herniated disc was made. Past history revealed that the patient had an illness diagnosed as rheumatic fever at the age of 6 years. Although symptoms were not typical, a heart murmur was heard. She was put on bed rest for 1 year, and has been restricted in activity ever since. She had two pregnancies without difficulty. There were no symptoms except mild exertional dyspnea. She did her housework without difficulty.

Physical examination was normal except for the chest and left leg. The right hemithorax was smaller than the left. On the right side the chest expansion was decreased, the percussion note was dull, and breath sounds were diminished. On the left the diaphragm was lower than

Fig. 3.

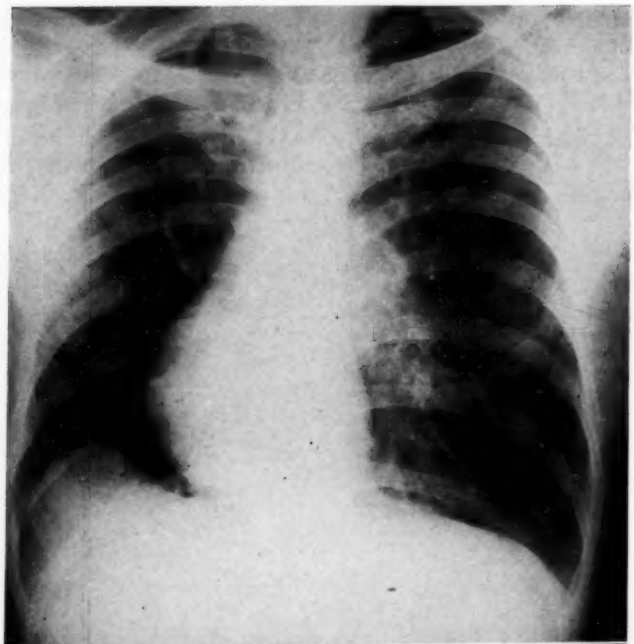

Fig. 4.

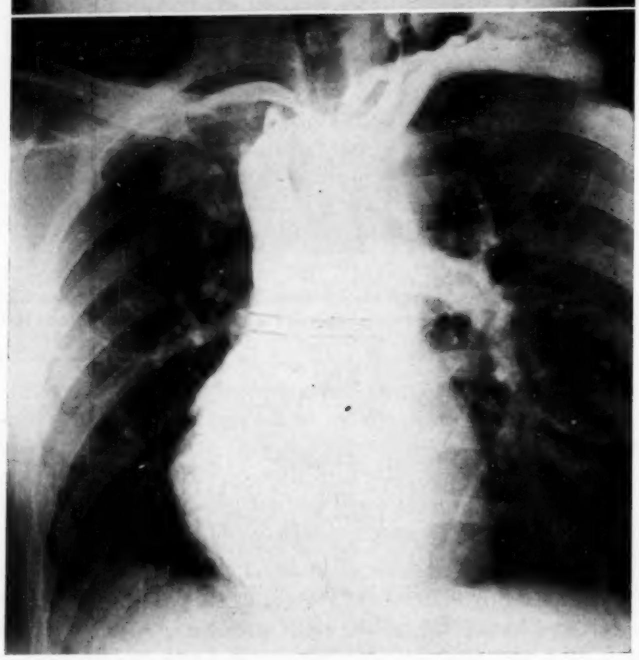

Fig. 3.—Case 2. Posteroanterior film of the chest in hypoplasia of the right pulmonary artery and hypoplasia of the right lung. The irregular and distorted vascular pattern on the right is noteworthy. Note also the compensatory dilation of the left pulmonary arterial trunk and its more peripheral branches.

Fig. 4.—Case 2. Angiocardiogram at 1.5 seconds. Compare the vasculature as seen here with the plain chest film in Fig. 5.

Fig. 5.—Case 3. Posteroanterior film of the chest in severe hypoplasia of the right pulmonary artery and the right lung. Note the diminished size and numbers of the pulmonary arteries on the right, together with the distorted, irregular distribution. In the base on the left the vasculature is tortuous and the vessels engorged. (*For Fig. 5 see opposite page.*)

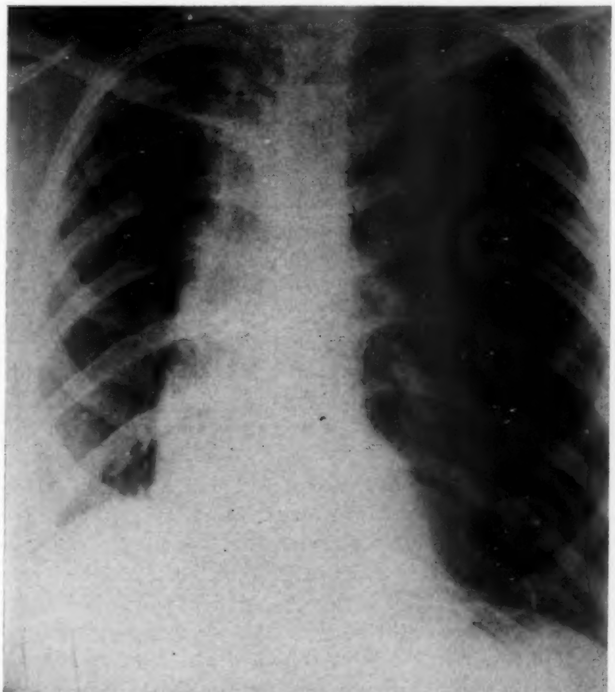

Fig. 5.

Fig. 6.

Fig. 5.—(*For legend see opposite page.*)

Fig. 6.—Case 3. Angiocardiogram at 1.5 seconds. The abrupt cutoff of the right pulmonary artery with only two small branches going to the upper and middle lobes is well seen. Noteworthy is the dilated, tortuous left pulmonary arterial trunk and peripheral divisions. See text for comment.

on the right and the percussion note was hyperresonant. The heart was shifted to the right. A Grade 3 systolic murmur was heard in the pulmonic area and transmitted along the left sternal border to the apex. The left leg was painful on raising it straight, and sensation was diminished along the lateral aspect of the thigh and leg.

The hemoglobin was 14 Gm., the red blood cell count was 4.35 million, and the white blood cell count was 6,700. The urinalysis was normal. An electrocardiogram was normal. Pulmonary function studies are shown in Table II.

A roentgenogram of the chest (Fig. 5) revealed a small right hemithorax, elevated right leaf of the diaphragm, and a shift of the heart and mediastinum to the right. The pulmonary blood vessels on the right were small and few in number, distorted and irregular. This was interpreted as a severely compromised arterial supply to the right lung. On the left there was engorgement and tortuosity of the pulmonary arteries.

An angiocardiogram is shown in Fig. 6. There is an abrupt cutoff of the diminished right pulmonary arterial trunk, with two small branches going to the upper and middle lobes. Part of the vascular pattern is presumed to fill from the bronchial arteries. The left pulmonary artery is considerably enlarged, tortuous, and with areas of narrowing, which could be due either to stenoses or to twisting of the vessels.

The patient made an uneventful recovery after her lumbar laminectomy for an herniated disc. She was told that she did not have rheumatic heart disease and was advised to return to normal activity. At the time of a 2-month follow-up the patient was doing well.

CASE 4.—E. H., a 43-year-old housewife, was admitted to the University Hospitals for her first delivery. The pregnancy had been normal except for mild hypertension. Before the pregnancy the patient had been told that she had contraction of the right lung, which probably was caused by a severe lung infection in the past. She had had some exertional dyspnea all her life.

The physical examination was normal except for the chest. There was a small right hemithorax. The right diaphragm was elevated. The breath sounds were diminished over the right base. The left lung was hyperresonant. There were no râles, and the left diaphragm was normally placed. There was a Grade 1 systolic murmur along the left sternal border and at the apex of the heart. Pulmonary function studies were made and are reported in Table II. The hemoglobin was 12 Gm., and the white blood cell count was 12,900. The urinalysis was normal.

Roentgenograms of the chest (Fig. 7) demonstrated a shift of the heart and mediastinum to the right, herniation of the left lung anteriorly, and only minimal elevation of the right leaf of the diaphragm. Study of the pulmonary vasculature on the right revealed absence of the pulmonary arteries. The vasculature noted was small, and represented bronchial arteries. On the left the pulmonary arteries were moderately increased in size and density. Little tortuosity was noted.

Angiocardiograms demonstrated total absence of the right pulmonary artery and compensatory dilatation of the left branch and its divisions. There was slight tortuosity of the vessels on the left. On the last film in the series it was seen that the bronchial arteries were filled from the aorta.

CASE 5.—C. V., a 58-year-old white housewife, was admitted to University Hospitals for thyroid evaluation. She had noted shortness of breath on exertion, and excessive fatigue of 4 or 5 months' duration. A cough had been present for 2 years. As a child this patient had been "sickly" and unable to keep up with other children. She had pneumonia 4 years ago and has had frequent colds since. She had lost 10 pounds in the preceding year.

Physical examination revealed the patient to be thin. She appeared chronically ill. The right hemithorax was small, expansion was decreased, and the right diaphragm was elevated. The diaphragm on the left was depressed. The breath sounds were good on the left, but decreased on the right. There were scattered râles throughout both lung fields. Ther percussion note was dull over the right lung. The heart was shifted to the right. No murmurs were heard.

The hemoglobin was 13 Gm., the white blood cell count was 11,650, and the differential count was normal. The urinalysis was normal. An electrocardiogram was normal. Pulmonary function studies are reported in Table II.

Roentgenograms of the chest taken 5 years apart are shown in Fig. 8. They reveal no change in the diminished size of the right hemithorax, in the shift of the heart and the mediastinum to

the right, nor in the findings of bronchiectasis on the right. The vascular pattern was not seen on the right, but on the left it was increased in size and density. Initially, we thought that the findings represented a lung destroyed by chronic bronchiectasis. Bronchograms revealed extensive bronchiectasis, but no statement regarding the anatomy of the lung could be made. An angiocardiogram was made and is shown in Fig. 9. The right main pulmonary arterial trunk is present, but is abruptly cut off. There are no vessels going to the right lung. The left pulmonary arterial trunk is dilated, but the peripheral branches are normal.

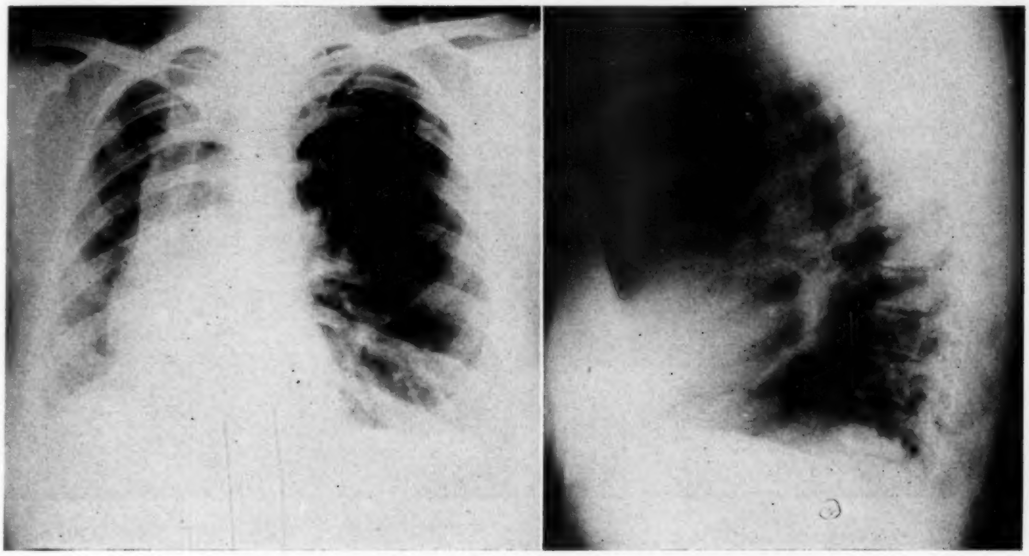

Fig. 7.—Case 4. Posteroanterior and lateral films of the chest in total absence of the right pulmonary artery. Note that there is nothing that can be called pulmonary arteries on the right. The tiny vasculature is bronchial in nature.

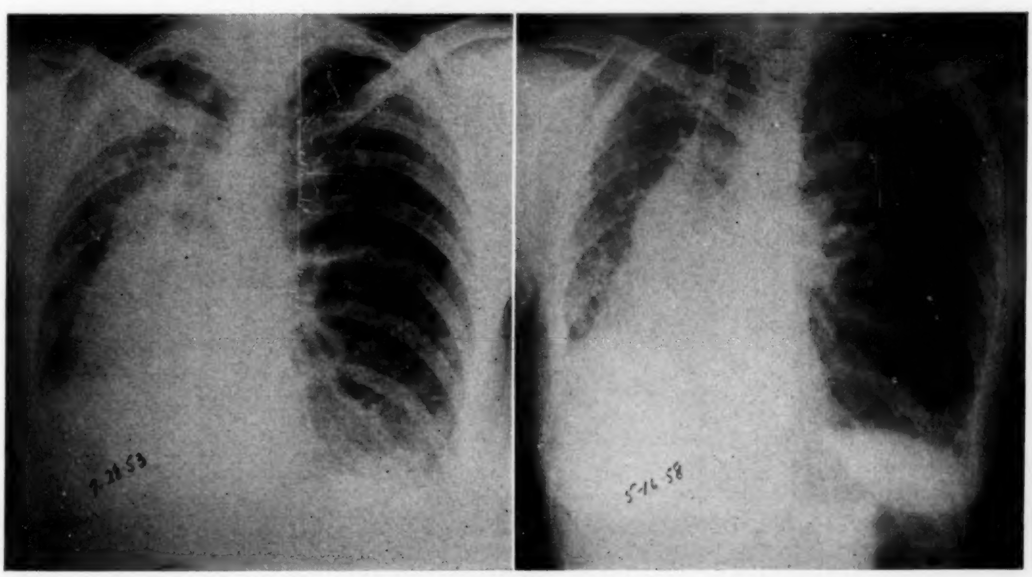

Fig. 8.—Case 5. Posteroanterior films of the chest taken 5 years apart. Case of total absence of the right pulmonary artery associated with bronchiectasis.

CASE 6.—R. P., a 7-year-old boy, was admitted to University Hospitals for investigation of his right lung. He had had pneumonia following measles 5 months earlier. A chest film at that time was interpreted as showing partial collapse of the right lung. The boy became asymptomatic, but a repeat chest x-ray film still showed collapse of the lower right lung; therefore, his doctor referred him to University Hospitals.

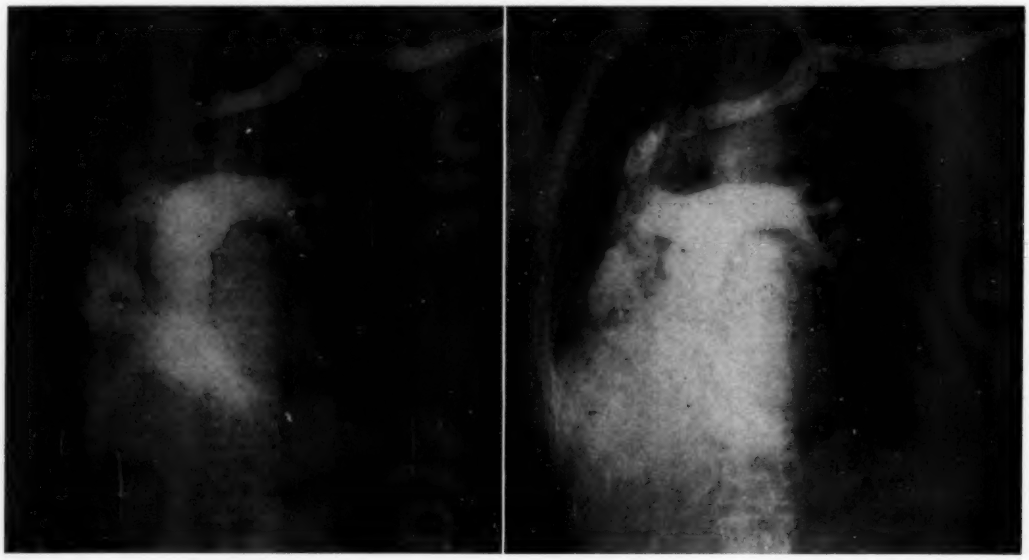

Fig. 9.—Case 5. Angiocardiograms at 3 and 4 seconds, demonstrating total absence of the right pulmonary artery.

Fig. 10.—Case 6. Posteroanterior film of the chest in hypoplasia of the right lung. Note the absence of pulmonary vascular markings on the right, indicating aplasia of the pulmonary artery.

On admission, his physical examination was normal except for the chest. There was decreased expansion on the right, with droop of the right shoulder. On percussion there was dullness over the right lung and hyperresonance over the left lung. Breath sounds were decreased on the right. The heart and mediastinum were shifted to the right. No cardiac murmur was heard.

The hemoglobin was 13.5 Gm., the red blood cell count was 4.6 million, and the white blood cell count was 12,800, with a normal differential count. The urinalysis was normal.

A posteroanterior film of the chest is shown in Fig. 10. This demonstrates the shift of the heart and trachea to the right, the narrowed intercostal spaces, and the lack of aeration of the right lung except at its base. No pulmonary vasculature can be discerned on the right. There is compensatory emphysema on the left. The bronchogram demonstrated anomalous bronchial and alveolar structures. Incidentally, there were three anomalous dorsal vertebrae. These are commonly associated with anomalies of the lung.[25]

Our final impression was anomalous development of the right lung and absent right pulmonary artery. Since the patient was asymptomatic, no treatment was felt necessary.

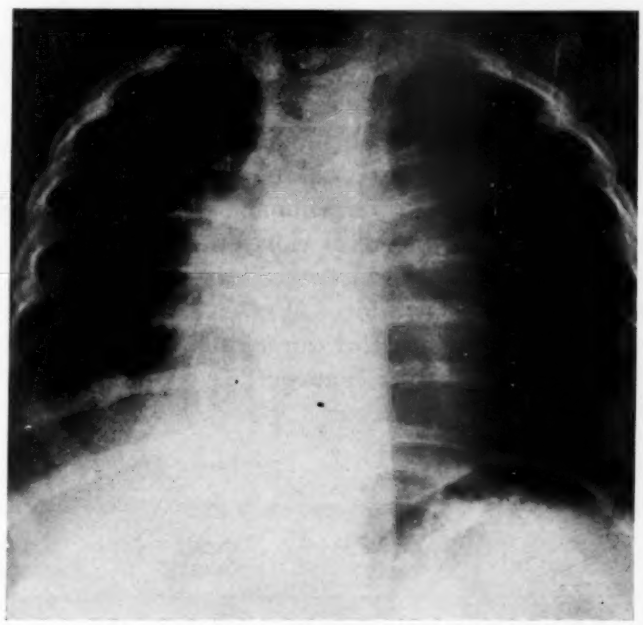

Fig. 11.—Case 7. Hypoplasia of the right lung with the pulmonary artery being only mildly hypoplastic.

Case 7.—R. L., a 7-week-old boy, was admitted to University Hospitals with the chief complaint of increasing dyspnea. He had had respiratory difficulty since birth, and did not eat well. One week before admission he became very dyspneic, choked on orange juice, and developed cyanosis. Chest x-ray films taken at that time were interpreted as showing atelectasis of the right lung. Treatment with oxygen and Alevaire gave some clinical improvement, but the chest findings did not change. There was no fever or cough.

On admission, the physical examination was normal except for the chest. The patient had marked sternal retraction with inspiration, and a small right hemithorax. On percussion there was dullness over the right lung and hyperresonance over the left lung. The breath sounds were decreased on the right side of the chest. The heart was shifted to the right, but it was not enlarged and no murmurs were heard.

The hemoglobin was 10.6 Gm., the white blood cell count was 11,100, the differential count was normal. The urinalysis was normal.

A posteroanterior view of the chest (Fig. 11) revealed a diminished volume of the right lung, with elevation of the diaphragm, slight shift of the trachea, and a more pronounced shift of the heart to the right. A pulmonary artery with branches to the upper and lower lobar areas was noted. Little or no vasculature was noted in the right mid-lung field.

The patient's next admission to the hospital was at the age of 6 months. He had done well except for two respiratory infections. Repeat chest roentgenograms showed no change. The diagnosis was unchanged. He was discharged and was requested to return in 4 months for bronchograms. They revealed hypoplasia of the right lung.

Our final impression was hypoplasia of the right lung and hypoplasia of the right pulmonary artery.

DISCUSSION

The old maxim, "One sees only that which he is seeking," holds true in this presentation of cases of anomalous pulmonary arteries. The diagnosis of this condition is initially a radiographic one, and for that reason radiologists must be aware of it. As in our experience, the condition may be confused with atelectasis due to obstruction of a portion of a lung by foreign body or carcinoma. Detection of diminshed or absent pulmonary arteries can be made only when there is familiarity with the normal pulmonary arterial attenuation pattern. A careful study of the pulmonary vasculature on the two sides is the essential factor in diagnosis, since there are variations in the amount of shift of the heart and mediastinum, and in the degree of elevation of the diaphragm. In severe hypoplasia or total aplasia, compensatory dilatation of the pulmonary arteries on the opposite side may be striking. We have no evidence that pulmonary hypertension has developed in any of our patients, although the tortuous left pulmonary artery as seen in Fig. 6 may be due either to medial sclerosis or to elongation and tortuosity of the vessels.

TABLE I. PULMONARY

	CASE 1 (MADOFF)	CASE 2 (SMART)	CASE 3 (MAIER)	CASE 4 (MAIER)
Inspiratory Capacity (ml.)	1,890 (79%)			
Expiration Reserve Volume (ml.)	500 (63%)			
Vital Capacity (ml.)	2.390 (75%)	2,350 (Left) 2,800 (Right)	Normal	—
Residual Volume (ml.)	730 (92%)		Slight increase	Increase
Functional Residual Capacity (ml.)	1,230 (78%)			
Total Lung Capacity (ml.)	3,120 (79%)		Normal	
RV/TLC Ratio	23			
Maximal Breathing Capacity (L./min.)	62 (70%)		Slight decrease	50%
% N_2 at end of 7 min.	1.41			
Timed Vital Capacity	Normal			
Ventilation (L./min.)				Hyperventilation at rest
Air	9.350 (200%) 249 (117%)			
Oxygen	7.480 (160%) 235 (110%)	390 c.c./min. (Right) 0 c.c./min. (Left)		
Diffusing Capacity (ml./min./mm. Hg)				
Arterial Oxygen Saturation—Air (%)	Normal	Not done	Normal	Normal
Arterial P_{CO_2}	Not done	Not done	Normal	Normal

Routine angiocardiograms are not necessary for diagnosis, unless there is obliteration of the vascular pattern by bronchiectasis (Fig. 8) or some other condition. The presence, however, of compensatory dilatation of the pulmonary vasculature on the opposite side may suggest that there is decreased or absent blood supply to the involved lung.

Pulmonary Function Studies.—Ten patients with isolated absence or hypoplasia of a pulmonary artery have had partial pulmonary function studies made by others. These findings are summarized in Table I. The essential findings were normal or slightly decreased vital capacity, maximum breathing capacity, and residual volume. Only four patients had the total lung capacity measured, with three being normal and one being decreased. The RV/TLC ratio was normal in two and increased in two. Distribution of inspired air was measured in one patient by the 7-minute N_2 washout method and was normal. The diffusing capacity was normal in the one patient in whom it was measured. Arterial oxygen saturation was normal in five and slightly decreased in three patients. The arterial P_{CO_2} was normal. Evidence of hyperventilation was present in four of the six patients tested.

Pulmonary function studies were done on three of our patients. Patient J.P. had severe hypoplasia of the right pulmonary artery and lung. Patient E.H. had total agenesis of the right pulmonary artery. Patient C.V. had total absence of the right pulmonary artery and associated bilateral bronchiectasis. None of these patients had pulmonary insufficiency for oxygenation or elimination of carbon dioxide. The lung volumes in E.H. and J.P. were essentially normal. Reduced lung volumes in C.V. may have been caused by bronchiectasis. All three patients were hyperventilating at the time of study, as measured by the minute volume of ventilation. Distribution of inspired air was normal in all

FUNCTION STUDIES

CASE 5 (STEINBERG)	CASE 6 (STEINBERG)	CASE 7 (STEINBERG)	CASE 8 (ELDER)	CASE 9 (ELDER)	CASE 10 (ELDER)
70%	2,820 (102%)	4,801 (105%)	2.9 (78%)	2.9 (69%)	3.3 (76%)
	1,803 (214%)	1,082 (95%)			
	4,623 (3,608)	5,883 (5,727)			
	39 (23)	18 (20)			
Normal	67 (83%)	162 (108%)	66 (87%)	125 (119%)	113 (65%)
			72%	85%	65%
	3.8	3.6	11.8 Right (83%) Left (17%)	9.6 Right (77%) Left (23%)	
		24			
—	93.2	98.8	89%	93%	95%
—	45	43	—	—	—

three patients. Maximal flow rates were somewhat low in all patients, but the maximal breathing capacity was normal. All patients had lower alveolar P_{CO_2} than arterial P_{CO_2}. This can be explained by the fact that one lung has very little vascular supply; therefore, less carbon dioxide is expired than on the normal side. Diffusion was measured in E.H. and J.P., and was low. This could be expected in the absence of the diffusing capacity of one lung, and confirms the findings of Ogilvie, Forster, Blakemore, and Morton[24] in one patient with a pneumonectomy and in another patient with an obstructed right pulmonary artery. The fact that the lung volumes remain normal suggests that the normal lung is capable of expanding to fill the thorax. These patients had little compromise of normal lung function. However, superimposed disease, as illustrated by bronchiectasis in C.V., may cause marked abnormalities in pulmonary function.

TABLE II. PULMONARY FUNCTION STUDIES AND ARTERIAL BLOOD STUDIES

	NORMAL VALUES	PATIENTS		
		J. P. (CASE 3) F, 44	E. H. (CASE 4) F, 43	C. V. (CASE 5) F, 58
Inspiratory Capacity (ml.)	80-120%	1,690 (59%)*	2,270 (89%)	700 (34%)
Expiration Reserve Volume (ml.)	80-120%	1,140 (119%)	510 (61%)	370 (54%)
Residual Volume (ml.)	80-120%	2,020 (173%)	1,420 (138%)	1,500 (62%)
Total Lung Capacity (ml.)	80-120%	4,850 (97%)	4,200 (95%)	2,570 (50%)
Vital Capacity (ml.)	80-120%	2,830 (74%)	2,780 (82%)	1,070 (39%)
RV/TLC Ratio	—	42	34	58
Minute Volume				
Air (L./min.)	6.0-9.0	9.6	9.2	12.1
Single Breath N_2 Test (% N_2)	0.0-1.5	1.9	1.5	—
% N_2 at end of 7 sec. of breathing oxygen	0.0-2.5	—	—	1.1
Maximal Breathing Capacity (L./min.)	80-120%	72 (75%)	90 (103%)	52 (87%)
Maximal Expiratory Flow Rate (L./min.)	400-600	—	152	83
Maximal Inspiratory Flow Rate (L./min.)	400-600	135	214	76
Diffusing Capacity (ml./min./mm. Hg)	20-40	18	16	—
Arterial Oxygen Saturation				
Breathing Air (%)	96-99	100% + 0.53	100% + 0.11	98.00%
Breathing 100% Oxygen	100% + 2.00 vol. %	100% + 1.94	100% + 1.82	100% + 2.53
Arterial P_{CO_2}				
Breathing Air (mm. Hg)	38-42	35	37	39
Alveolar P_{CO_2}				
Breathing Air (mm. Hg)	38-42	30	27	27

*The figures with a % sign in parentheses refer to the per cent of predicted normal.

Clinical Findings.—When one pulmonary artery is absent and the heart is normal, it is usually the right pulmonary artery which is affected. Maier[13] and Emanuel[26] have reviewed the literature in this respect. In our series this was true, six occurring on the right as compared with only one on the left. When the left pulmonary artery is absent there is frequently an associated cardiovascular anomaly as reported by Vaughan[27] and Steinberg.[11]

The occurrence of a cardiac murmur might be emphasized in these patients with isolated absence or hypoplasia of one pulmonary artery. The murmur is

usually heard best in the pulmonic area or along the left sternal border; it may be widely transmitted; it may be as loud as Grade 3 or 4 in intensity, and a thrill may be present. The pulmonic second sound may be slightly accentuated and is frequently split. A possible explanation for this cardiac murmur is dilatation and tortuosity of the patent pulmonary artery, with increased blood flow through it. A mistaken diagnosis of cardiac disease may occur, as in our Patient J.P., with needless restrictions being imposed on the patient.

All seven patients were relatively asymptomatic except for mild exertional dyspnea and respiratory infections. Hemoptysis did not occur in any of these patients, although bronchial arterial communications were seen by angiocardiography. In several instances the patients had been told that they had an abnormal chest x-ray film. In no case had the correct diagnosis been suspected prior to hospitalization at the University Hospitals.

SUMMARY

1. Reported here are seven cases of unilateral absence or hypoplasia of a main branch of the pulmonary artery in which the diagnosis was made before autopsy or surgical exploration.

2. Reported pulmonary function studies in this condition have been reviewed. We measured pulmonary function in three of our patients, one of whom had associated bronchiectasis. There was no evidence of pulmonary insufficiency for oxygenation or elimination of carbon dioxide. All patients hyperventilated at rest, and had decreased alveolar P_{CO_2} with normal arterial P_{CO_2}. Lung volumes and mechanical tests were normal except in two patients in whom they were slightly decreased. In the patient with bronchiectasis, however, great decrease in lung volumes and mechanical tests suggested lessened respiratory reserve.

3. Cardiac murmurs were heard in several patients without evidence of intracardiac disease, presumably from dilatation, distortion, and tortuosity of the other pulmonary artery.

4. Careful study of the pulmonary vasculature in plain films of the chest should suggest hypoplasia or agenesis of a pulmonary artery without angiocardiography being required. Hypoplasia or agenesis is frequently mistaken for atelectasis.

5. Angiocardiography should be reserved for patients with associated lung disease, such as bronchiectasis which obscures the pulmonary vessels.

6. Agenesis of a pulmonary artery may be associated with complete absence of the lung, but more commonly is associated with hypoplasia.

7. Hypoplasia of a pulmonary artery is, in our experience, always associated with a maldevelopment of the lung. The extent of the anomaly varies considerably.

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Variations in Blood Pressure in the Two Arms of Urban Africans

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In a recent review of the literature on the variation in blood pressure in the two arms, Katz[1] states: "Concerning the question of variation of blood pressure readings in the two arms, very little is found in the recognized textbooks and journal literature beyond the passing reference to the fact that in cases of aortic aneurysm the pressures may be unequal. It has been demonstrated that many 'normal' people may have a different pressure in each arm. The literature fails to reveal more than a few articles on this aspect of blood pressure measurement. . . . It would seem that inequalities in the blood pressure between both arms is regarded either as too slight to be of consequence, or if more than slight to be inconsequential. . . . With the exception of Amsterdam and Amsterdam,[2] the authorities cited, although acknowledging variation of readings in the two arms, regard them as inconsequential or not frequent enough to be of great concern."

It has been found generally that there is a preponderance of pressure in the right arm, i.e., when there is a variation, the higher reading is more commonly obtained on the right arm. The reasons for a variation in normal persons have been largely a matter of conjecture.

There is disagreement about the relationship between the level of the blood pressure and the variation in pressure between the right and left arms. Although some studies have indicated that there is more variation in persons with a higher blood pressure,[3-5] this has not been a constant finding.[6]

It was hoped that a study of the right-left disparity in an African population might throw further light on this phenomenon, and, in particular, on its possible universality. In addition, the relationship of right-left variation to the level of blood pressure, age, and sex was investigated.

This study was part of a larger nutrition-hypertension project begun in 1958, by the Department of Social, Preventive and Family Medicine, University

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Received for publication March 4, 1959.

*State College of Washington, Pullman, Wash. Work done during the tenure of a Research Fellowship of the U. S. Public Health Service, 1957-1959, and with the financial assistance of the U. S. Public Health Service, the Program of African Studies, Northwestern University, and the State College of Washington.

of Natal. It was carried out on 319 Zulu adults (96 males and 223 females), who were over 18 years of age, and who were drawn from a randomly selected larger sample comprising all the residents of every seventh home in an African housing scheme in Durban. As will be reported later, there is a high prevalence of hypertension in this community. The sample manifested a high frequency of signs of malnutrition, and five persons, though ambulant, were under treatment for congestive cardiac failure.

Persons participating in the study were transported from their homes to the Institute of Family and Community Health for examination. Blood pressures were determined with the subjects seated, using a Baumanometer, the diastolic pressure being equated with the disappearance of the sound. Consecutive readings were taken on the two arms, the reading on the left arm being taken first in 136 persons and that on the right arm, first in 183 persons. All the readings were made by the same physician (C. S.), except in three instances.

RESULTS

The reading in the first arm tended to be higher than the reading in the second arm. The proportion of persons whose first-arm reading was higher (by 10 mm. Hg or more) was significantly greater than the proportion whose first-arm reading was lower (by 10 mm. Hg or more). This applied to both the systolic and the diastolic pressures (Table I). When the systolic pressure was higher on one side, there was a significant tendency for the diastolic pressure to be higher on the same side, whichever arm was measured first ($P < 0.001$).

In seeking evidence of a right-arm or left-arm preponderance, it was necessary to take into account the chronological factor. It was found that there was a slight, but significant, preponderance in the right arm. This was indicated by the fact that higher first-arm systolic and diastolic readings were more common, and lower first-arm readings less common, when the right-arm pressure was taken first than when the left-arm pressure was taken first. Such a difference must indicate a preponderance on the right side. This finding was statistically significant for the systolic pressure but not for the diastolic pressure (Table II).

On examining the relationship between the level of the blood pressure and the variation in pressure between the two arms, it was found that the preponderance on the right side occurred in normotensive persons but not in hypertensive persons; in the latter there was a significant preponderance on the left side.

In normotensive persons, appreciably higher systolic and diastolic readings in the second arm were less common when the right-arm pressure was taken first than when the left-arm pressure was taken first. This difference was statistically significant for the systolic pressure but not for the diastolic pressure.

However, the reverse finding applied to hypertensive persons, among whom appreciably higher systolic and diastolic readings in the second arm were more common when the initial reading was on the right arm. This difference was significant for the diastolic pressure but not for the systolic pressure (Table III).

TABLE I. VARIATION IN BLOOD PRESSURE IN CONSECUTIVE ARM READINGS

PRESSURE	NUMBER OF PERSONS	FIRST READING HIGHER BY 10 MM. HG OR MORE (%)	DIFFERENCE LESS THAN 10 MM. HG (%)	FIRST READING LOWER BY 10 MM. HG OR MORE (%)
Systolic	319	31.4*	51.7	16.9*
Diastolic	319	20.4**	65.2	14.4**

*P < 0.001
**P < 0.05

TABLE II. VARIATION IN BLOOD PRESSURE IN CONSECUTIVE ARM READINGS, IN RELATION TO THE ORDER OF MEASUREMENT

PRESSURE	NUMBER OF PERSONS	FIRST-ARM READING HIGHER THAN SECOND		NO DIFFERENCE (%)	FIRST-ARM READING LOWER THAN SECOND		P AS DETERMINED BY CHI-SQUARE TEST
		10 MM. Hg OR MORE (%)	1-9 MM. Hg (%)		1-9 MM. Hg (%)	10 MM. Hg OR MORE (%)	
Systolic							
Right arm first	183	32.7	27.3	15.3	12.0	12.5	P < 0.05
Left arm first	136	29.4	18.4	11.8	17.6	22.7	
Diastolic							
Right arm first	183	20.7	31.1	11.5	21.9	14.8	P > 0.1
Left arm first	136	19.9	23.6	9.5	33.1	13.9	

TABLE III. VARIATION IN BLOOD PRESSURE IN CONSECUTIVE ARM READINGS, IN RELATION TO THE INITIAL LEVEL OF BLOOD PRESSURE

	NUMBER OF PERSONS	PER CENT WITH HIGHER BLOOD PRESSURE (BY 10 MM. Hg OR MORE) IN SECOND ARM	
		SYSTOLIC	DIASTOLIC
Normotensive Persons			
Right arm first	125	11.2*	12.8
Left arm first	106	26.4*	17.0
Hypertensive Persons			
Right arm first	58	15.5	19.0**
Left arm first	30	10.0	3.8**

*P < 0.01
**P < 0.02

For the purposes of this study, persons with initial systolic blood pressure readings of over 160 mm. Hg, or diastolic readings over 96 mm. Hg were arbitrarily designated as hypertensive; while persons with initial systolic readings of 160 mm. Hg or less, and diastolic readings of 96 mm. Hg or less were regarded as normotensive.

A comparison of the hypertensive with the normotensive persons in relation to the prevalence of appreciable disparities between the two pressures showed conflicting findings. When the pressure in the right arm was taken first, large variations in the systolic and diastolic pressures were significantly more common among hypertensive than among normotensive persons. However, these differences were not found when the pressure in the left arm was taken first (Table IV).

TABLE IV. PREVALENCE OF DISPARITY OF 10 MM. HG OR MORE BETWEEN CONSECUTIVE ARM READINGS, IN RELATION TO THE LEVEL OF BLOOD PRESSURE

	NUMBER OF PERSONS		PER CENT WITH DISPARITY OF 10 MM. Hg OR MORE		
	NORMOTENSIVE	HYPERTENSIVE	NORMOTENSIVE	HYPERTENSIVE	P
Right arm first					
Systolic	125	58	40.8	58.6	<0.05
Diastolic	125	58	31.2	46.6	<0.05
Left arm first					
Systolic	106	30	50.0	60.0	> 0.2
Diastolic	106	30	35.8	26.7	> 0.3

DISCUSSION

Although frequent and extensive discrepancies were found between the blood pressure readings in the two arms, it is not possible to conclude that they reflect differences between right arm and left arm rather than differences between first arm and second arm. However, the finding that there is a slight tendency toward a preponderance of pressure in the right arm indicates that there is a degree of variation between the two arms which is independent of the chronological factor.

This finding of a preponderance of pressure in the right arm confirms the findings of other workers.[2-5,7,8] We have not been able to find published evidence of a tendency toward a preponderance of pressure in the left arm in hypertensive persons similar to that seen in this sample. However, Hoyer,[8] in a study of 600 unselected bed patients, made the interesting observation that of the 6 per cent of his patients who had a preponderance of both systolic and diastolic pressures in the left arm, most had "organic heart disease." The subject of a preponderance of one side over the other in hypertensive persons merits further study.

Caution should be used in generalizing from our findings, because ethnic differences have been shown to exist in the anatomy of the cardiovascular system.[9,10] It is not impossible that ethnic differences may have some relationship to variations in blood pressure.

The implications for the practicing physician of the variation in blood pressure readings in the two arms have been discussed by Rueger.[4] As he states, "the difference might be of vital importance . . . in the case of examination for life insurance, employment or military service."

Our finding of a preponderance of pressure in the right arm in normotensive persons, and a preponderance of pressure in the left arm in hypertensive persons, bears out the importance of the recommendation that the blood pressure of a new patient be taken in both arms.[11]

SUMMARY

1. A study was carried out on the variations in blood pressure in the two arms of 319 urban Zulu adults.

2. In the sample as a whole, evidence was found of a tendency toward a preponderance of pressure in the right arm.

3. This tendency was found in normotensive persons but not in hypertensive persons; in the latter there was a tendency toward a preponderance of pressure in the left arm.

4. Age and sex were not related to interarm variations.

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Complications of Transbronchial Left Atrial Puncture

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Needle puncture of the left atrium or left ventricle for the purpose of hemodynamic study has become an accepted and useful procedure. It has not yet been clearly established which of the several techniques described is safest. Since none of the methods described is free from hazard, it would seem worth while to report experiences with each method for subsequent comparative study.

While puncture of the left ventricle for diagnostic purposes was reported in man as long ago as 1936 (Nuvoli[1]), left atrial puncture for pressure studies was first reported by Facquet[2] in 1952. The transbronchial approach was used. This method was further developed by Allison and Linden[3,4] in England, and was extensively used by Morrow[5,6] and his associates in this country.

Björk[7] introduced the right paravertebral transthoracic approach to the left atrium in 1953, and Radner,[8] the suprasternal approach in the same year. The former technique has been further developed and popularized in this country by Fisher.[9] It has been the most widely used technique of the three described. The reported experience by the suprasternal route has not been large.

TECHNIQUE

We have followed the technique described by Morrow.[6] An arterial needle is inserted into a femoral or brachial artery for recording of peripheral arterial pressure, and with topical anesthesia, a bronchoscope is passed into the left main bronchus. The patient's head is depressed so that the bronchoscope does not point posteriorly. The Morrow transbronchial needle* is inserted under direct vision through the anteromedial wall of the left main bronchus at a point 1 or 2 cm. distal to the carina (Fig. 1). The needle passes posterior to the pulmonary artery and enters the left atrium 2 to 4 cm. deep to the bronchial wall. In many instances the extrapericardial space between the pericardial reflections on the posterior wall of the left atrium is entered. However, in autopsy dissections, we have observed that the free pericardial space is traversed in the majority of cases, usually through the oblique pericardial sinus (Fig. 2). Pressures are recorded with a P23D Statham transducer connected to the side arm of the needle. A fine-caliber polyethylene (I.D. .023", O.D. .038")† or polyvinyl (I.D. .020", O.D. .036")* catheter is then passed through the needle into the left atrium and across the mitral valve into the left ventricle. Pressure recordings are made through the catheter, with care being taken to obtain a withdrawal curve

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Received for publication March 14, 1959.
*Manufactured by Becton-Dickinson Company, Rutherford, N. J.
†Manufactured by Clay-Adams Company, Inc., New York, N. Y.

across the mitral valve. Unless further studies with indicator or radiopaque dyes are planned, the procedure is terminated by removing the catheter and needle. The tracheobronchial tree is aspirated free of blood and the bronchoscope removed. The patient is observed closely for the next 24 hours, and antibiotics are routinely administered.

RESULTS

In 76 transbronchial left atrial punctures the left atrium was entered in every instance but one, in which the ascending aorta was punctured. It was impossible to pass the catheter into the left ventricle in 18 cases. The inability to enter the left ventricle was attributed in part to the presence of significant mitral insufficiency in 10 of these cases. There have been 3 important complications, with one fatality.

Early in the series, a polyethylene catheter became knotted in the left atrium and was removed during thoracotomy following the procedure. The patient made an uneventful recovery.

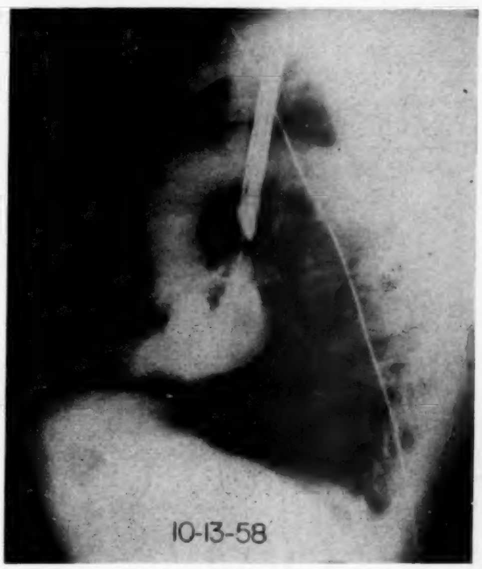

Fig. 1.—Cardioangiogram, obtained by left atrial route, demonstrating position of bronchoscope and left atrial needle.

Late in the series, a patient developed acute cardiac tamponade 1 hour after an uneventful combined left and right heart catheterization. The mean left atrial pressure in this patient was 30 mm. Hg. It was necessary to aspirate the pericardial cavity twice, with the removal of 50 and 25 c.c. of blood, respectively. The patient recovered completely.

The sixty-seventh patient in the series died 18 hours after catheterization. This was a 31-year-old man with mitral stenosis and insufficiency who had had an unsuccessful commissurotomy 2 years earlier at another institution. At that time his mitral valve was described as being fixed and calcified. The clinical course had been complicated by staphylococcic endocarditis the following year.

He was admitted for evaluation for open-heart surgery. Examination revealed the clinical findings of mitral stenosis and insufficiency, with marked cardiac decompensation. Left atrial puncture was performed uneventfully on Nov. 7, 1958. Mean left atrial pressure was 36 mm. Hg, and the pressure pulse sug-

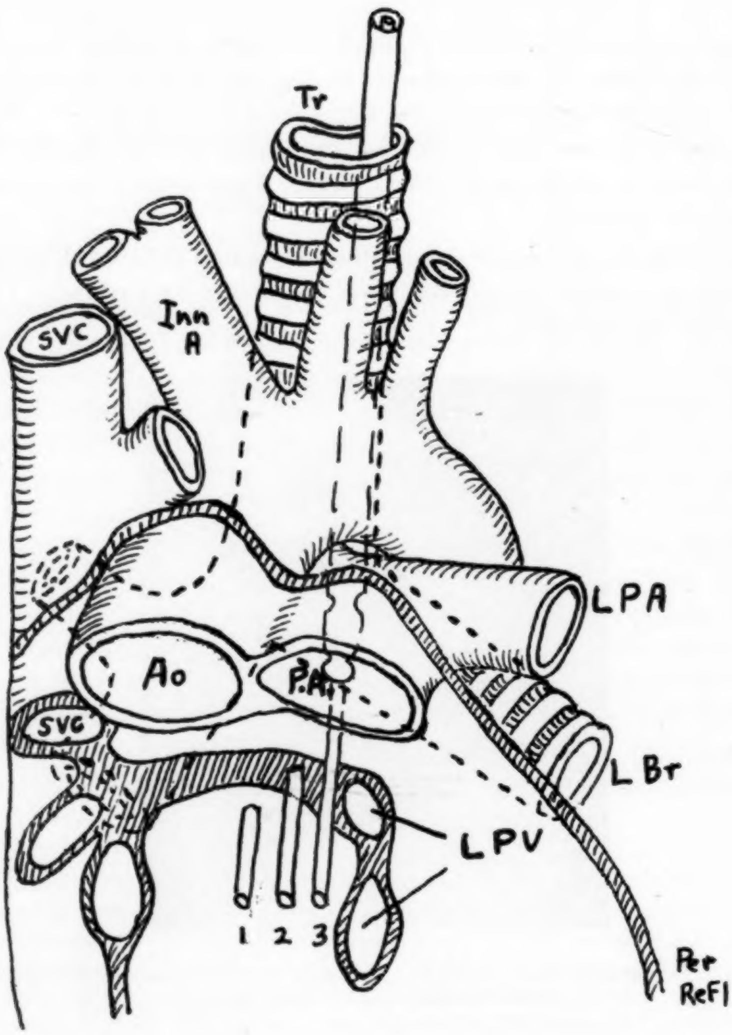

Fig. 2.—Diagram illustrating the three possible routes of the transbronchial needle between the left main bronchus and the left atrium: ***1*****, By way of the oblique pericardial sinus.** ***2*****, By way of the extrapericardial space (of variable extent) between the pericardial reflections on the posterior wall of the left atrium.** ***3*****, By way of the transverse pericardial sinus, behind the pulmonary artery.** ***Ao*****: Aorta.** ***Inn A*****: Innominate artery.** ***L Br:*** **Left main bronchus.** ***LPA:*** **Left pulmonary artery.** ***Per. Refl.:*** **Pericardial reflection and cut pericardium.** ***LPV:*** **Left pulmonary veins.** ***P.A.:*** **Pulmonary artery.** ***SVC:*** **Superior vena cava.** ***Tr:*** **Trachea.**

gested a predominantly stenotic lesion. It was not possible to pass a catheter through the mitral valve. There was considerable bleeding from the needle puncture of the left main bronchial wall, and the patient continued to expectorate bloody secretions for several hours after the procedure. Twelve hours later the

patient suddenly became comatose, and cardiac asystole occurred 7 minutes later. Cardiac massage resulted in a normal rhythm with less than 2 minutes of arrest, but the patient never regained consciousness, and expired 6 hours later. At autopsy no immediate cause of death was apparent, other than the calcific, immobile mitral valve with an orifice of 0.5 cm.^{2}. The pericardium was adherent, with no free pericardial space and no evidence of cardiac tamponade. There was no evidence of thrombotic formation in either the left atrium or ventricle. Unfortunately, permission to examine the brain was not obtained. The exact cause of death has not been completely explained, but cerebral embolization remains a possibility.

There were no other complications in this series.

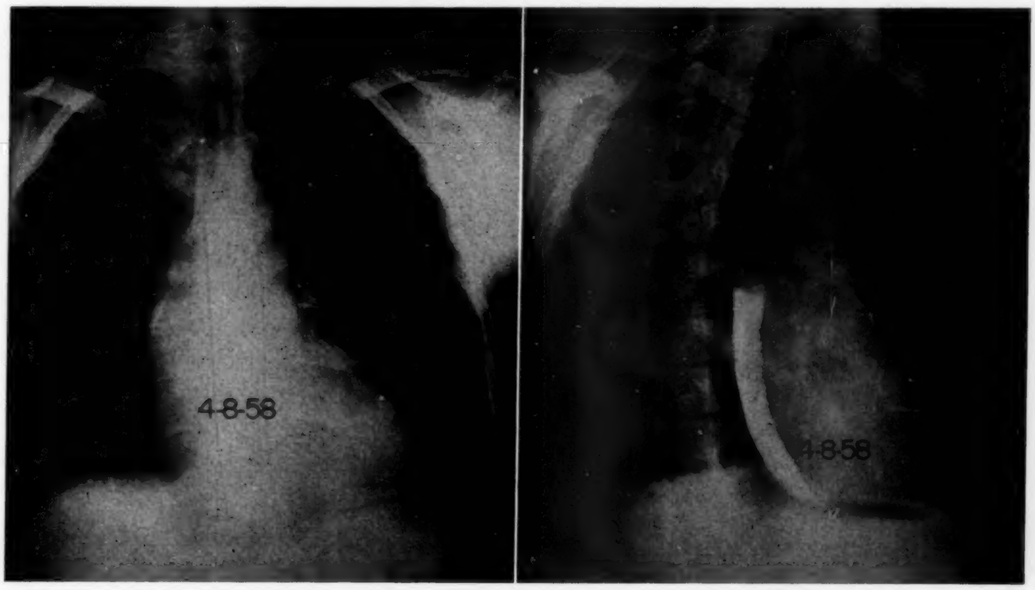

Fig. 3.—Posteroanterior and right anterior oblique chest films demonstrating small aneurysm of ascending aorta, punctured by transbronchial needle without complication.

DISCUSSION

In 2,178 collected cases of paravertebral left atrial puncture[6,10-21] 15 deaths were reported, a mortality rate of 0.69 per cent. In 1,472 collected cases of transbronchial left atrial puncture[6,22-24] the case herein described is the only known reported death, a mortality rate of 0.068 per cent. One other death, reported by Rubin and Shah,[23] was due to a drug reaction following the use of a combination of cocaine and Pontocaine for bronchoscopic anesthesia. Although atrial puncture was not performed, the death emphasizes the fact that the risk due to bronchoscopy must be added to that of left atrial puncture and catheterization. There have been no deaths following atrial puncture by the suprasternal route in 72 reported cases.[25,26]

As Fisher[9] has stated, the theoretical dangers of transthoracic left atrial puncture are many. The atrium is punctured at a depth of 10 to 14 cm. beneath

the surface of the skin, and in guiding the needle into the left atrium, one seeks to avoid the eighth intercostal artery, the right pleural cavity, lung, esophagus, right atrium, azygos vein, inferior vena cava, pulmonary artery, and ascending aorta. Certainly the worst of these dangers is intrapericardial puncture of the ascending aorta, with resulting acute cardiac tamponade. This is a hazard in the transbronchial method as well. In one patient with a small aneurysm of the ascending aorta (Fig. 3), systemic pressures were recorded during attempted left atrial puncture. The procedure was terminated uneventfully. Pate[27] reports a similar episode, resulting in acute tamponade, almost immediately after obtaining a pressure tracing characteristic of the aorta. Pericardiocentesis yielded 200 c.c. of fresh blood, with immediate clinical improvement and eventual recovery.

The theoretical dangers of the transbronchial approach appear to be fewer than those of the transthoracic. Because of the proximity of the left atrium to the left main bronchus the opportunity for puncturing organs other than the atrium is less than in the transthoracic approach. This is borne out by the scarcity of serious complications, and the lesser variety of complications of any kind, by this route. Septicemia and aspiration pneumonitis have not occurred in this or other reported series.

One complication of left atrial puncture, which does not seem to be avoidable by any route, is that of embolization from a thrombus in the atrium. This complication occurred twice, without fatality, in the series of 113 patients reported by Kavanagh-Gray and Drake,[17] who used the right transthoracic approach, and once in the group of 64 transbronchial left atrial punctures described by Rubin and Shah.[23] It proved fatal in one case reported by Bosher[28] in which the paravertebral avenue was used. Fortunately, it seems to be a rare occurrence.

Another complication common to both transbronchial and transthoracic paravertebral left atrial puncture is that of knotting of the intra-atrial catheter. The possibility of this occurring can be minimized by using only one catheter in the atrium at a time, by using stiffer catheters, and by limiting the total length of catheter passed into the atrial chamber. The shearing off of a length of catheter by the point of the intra-atrial needle has been reported by Musser and Goldberg[11] in 2 patients. The catheter fragments were removed at thoracotomy from the left atrium in one instance and the left ventricle in the other.

Other possible complications of transthoracic left atrial puncture include hemothorax, pneumothorax, cardiac tamponade, and mediastinal hematoma. The only one of these conditions reported after transbronchial atrial puncture is cardiac tamponade. This apparently occurs less frequently than with transthoracic puncture. It is of interest that in our series, as in that of Kavanagh-Gray and Drake,[17] the only case of clinical cardiac tamponade occurred without evidence of aortic puncture, and in combination with right heart catheterization. These authors felt that the heparin received through the right heart catheter during a prolonged procedure may well have contributed to the bleeding.

Although no complications have been reported by those utilizing the suprasternal approach to the left atrium,[25,26] the small-lumen needle required for this

technique is a distinct disadvantage. Since the needle traverses the aorta and pulmonary artery on its course to the left atrium, the small lumen is dictated by considerations of safety, but this means that samples cannot be withdrawn nor indicator dyes injected through the needle, nor can a catheter be passed into the left ventricle.[26] To circumvent this drawback, a needle is placed into the left ventricle through the anterior chest wall, thus adding the appreciable risk of left ventricular puncture to that of puncture of the left atrium.

The need for an experienced bronchoscopist has limited the popularity of transbronchial left heart catheterization, but despite this requirement, we feel that increased safety makes this technique the most desirable approach to the left atrium.

CONCLUSION

Seventy-six left atrial punctures by the transbronchial technique have been performed, with three complications, one of which resulted in a fatality. This is the first reported case of fatality following left heart catheterization utilizing this approach to the left atrium. Comparison has been made of the complications of the various avenues of approach to the left atrium. The technical aspects involved in the transbronchial, paravertebral, and suprasternal routes have been discussed. In spite of the fatality, the high rate of successful left atrial punctures combined with the low over-all morbidity and mortality with the transbronchial method makes us feel that it is the preferable technique for left atrial puncture.

ADDENDUM

After this manuscript had been submitted for publication, an additional 10 patients were subjected to transbronchial left heart catheterization, without complication. The use of the slightly stiffer Afford plastic polyvinyl catheter* through the transbronchial left atrial needle in place of the polyethylene catheter in these 10 patients greatly simplified the problem of catheterizing the left ventricle.

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Total Body Exchangeable Potassium and Sodium and Extracellular Fluid in Chronic Pulmonary Insufficiency

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In recent years, measurements of exchangeable body potassium,[1-4] exchangeable body sodium,[4-6] and extracellular fluid[4,6,7] have been carried out in a variety of disease states. Depletion of potassium, retention of sodium, and increased extracellular fluid have been reported in congestive heart failure[2,6] and in chronic debilitating diseases.[8,9] It appeared worth while to pursue these studies on patients with chronic pulmonary insufficiency in whom debility and cardiac failure are known to be frequent, and in whom the authors have often encountered digitalis sensitivity.[10,11] Since arterial blood gas and pH abnormalities are commonly encountered in these patients, it was also deemed advisable to attempt a correlation of these aberrations with measurements of exchangeable body potassium, exchangeable body sodium, and extracellular fluid.

MATERIALS AND METHODS

Forty-one subjects with chronic, diffuse, obstructive pulmonary emphysema and one with histologically proved chronic interstitial pulmonary fibrosis were studied. Total body exchangeable sodium and potassium were measured by radioisotope dilution techniques[12,13] as modified by one of the authors.[14] The isotopes Na^{24} and K^{42} were used simultaneously. Both plasma and a freshly collected sample of urine, collected at the end of a 24- to 40-hour equilibration period, were analyzed for radioactivity and for sodium and potassium. The measurements of total body exchangeable sodium and potassium were based on the assumption that the specific activities of the electrolytes in a freshly excreted sample of urine were equal to those of the plasma. Values obtained by this modification agreed with those achieved by the previously described methods.

Burch and associates[15] have shown that equilibration is not complete in 24 hours. However, the approach to equilibrium is exponential, so that exchange is practically complete at that time. The increased precision resulting from a longer equilibration period was not considered essential for the degree of alteration under study.

The volume of extracellular fluid was calculated from the Na^{24} blood concentration curve extrapolated to zero time. Berson and Yalow[16] demonstrated that in nonedematous subjects this method yields measurements agreeing with those obtained by inulin, sucrose, or corrected Br^{82}. In patients with large collections of extracellular fluid, such as ascites, edema, and pleural effusion, this technique underestimates the volume of extracellular fluid.

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Received for publication March 23, 1959.

Coincident with the final collection of blood for the radioisotope determination, arterial blood was collected under basal conditions. Determinations of gases and pH were made by standard techniques.[17-19] Ventilatory functions and lung volumes were performed by techniques previously described.[20-22] Control radioisotopic measurements were obtained in healthy medical student volunteers.

TABLE I. PULMONARY FUNCTION MEASUREMENTS

PATIENT	AGE	MBC (PER CENT PREDICTED)	VC (PER CENT PREDICTED)	1"VC (PER CENT VC)	RESIDUAL VOLUME		RV/TLC (%)
					OBS.	PREDICTED	
W.H.	67	16	45	24	—	—	—
J.H.	67	*	42	40	3,703	1,525	73
H.T.	61	17	30	35	—	—	—
A.H.	53	20	51	18	5,118	1,580	70
C.T.	60	20	55	26	5,239	1,440	74
H.H.	54	21	61	21	5,218	1,705	69
R.McC.	59	22	38	42	3,407	1,475	69
T.L.	62	24	50	20	5,898	1,633	78
E.E.	64	26	69	21	4,443	1,533	70
A.P.	57	27	50	36	4,629	1,570	67
C.W.	66	28	28	49	4,020	1,447	75
R.G.	60	28	30	31	4,741	1,725	79
W.B.	40	*	33	29	7,075	1,305	79
T.M.	64	30	54	28	4,207	1,655	65
T.W.	49	31	48	53	5,925	1,245	70
C.A.	62	31	50	28	5,593	1,595	71
C.G.	65	33	54	28	5,340	1,640	71
C.L.	59	34	49	23	2,426	1,550	54
M.W.	63	35	36	36	4,805	1,473	70
I.R.	68	35	56	24	3,310	1,515	60
H.B.	59	35	68	30	—	—	—
W.R.	51	35	102	25	4,320	1,680	55
O.C.	58	36	36	35	4,994	1,567	73
R.P.	64	38	54	32	4,900	1,430	70
G.D.	65	41	59	37	4,755	1,595	67
J.P.	59	42	100	30	3,592	1,687	43
R.Y.	49	43	39	43	3,213	1,150	67
M.M.	59	45	65	43	5,808	1,500	69
J.T.	57	60	70	35	4,731	1,665	53
L.O.N.	65	61	75	33	4,474	1,495	66
A.I.	63	61	105	45	3,830	1,565	61
C.M.**	64	104	79	48	1,512	1,550	36

*Too ill for satisfactory cooperation.
**Interstitial pulmonary fibrosis.

TABLE II. SUMMARY OF RESULTS OF RADIOISOTOPE DILUTION MEASUREMENTS

	DISEASED			CONTROL			
	NUMBER	MEAN	S.D.	NUMBER	MEAN	S.D.	
TBK (mEq./Kg.)	42	32.5	7.2	29	46.3	4.3	$P < 0.01$
TBNa (mEq./Kg.)	37	50.3	9.5	11	41.9	4.7	$P < 0.001$
ECF (c.c./Kg.)	22	232.7	67.4	7	162.6	17.3	$P < 0.001$

RESULTS

The pulmonary ventilatory and volume measurements are given in Table I. Satisfactory determinations were carried out in 33 subjects. Maximum breathing capacity (MBC) ranged from 17 to 61 per cent of predicted values in the emphysematous subjects. It was 104 per cent of predicted values in the patient with interstitial pulmonary fibrosis (C. M.). Vital capacities ranged from 30 to 105 per cent of predicted values. The one-second vital capacities (1″VC) showed the expected slowing. The ratios of residual volume to total lung capacity (RV/TLC) were above 50 per cent, and the residual volumes were considerably increased whenever these were determined in patients diagnosed clinically as having chronic obstructive pulmonary emphysema.

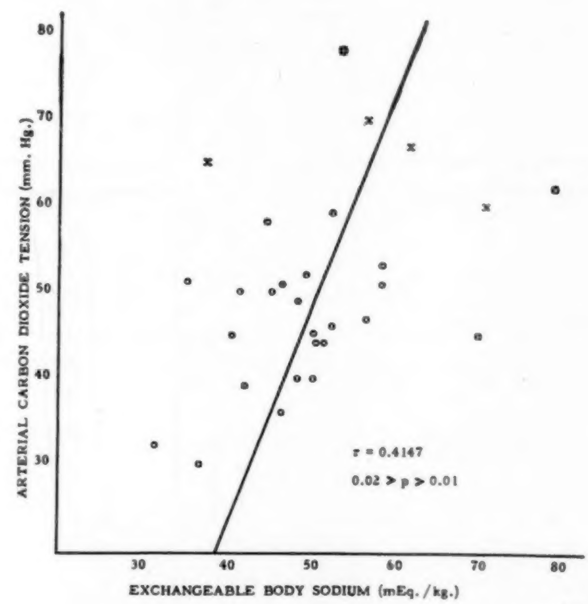

Fig. 1.—Linear relationship between exchangeable body sodium and arterial carbon-dioxide tension. ***X*** **indicates the presence of congestive failure.**

The results of the radioisotope dilution measurements are summarized in Table II. The mean total body exchangeable potassium (TBK) in 42 subjects was 32.5 mEq./Kg., contrasted with a control value of 46.3 mEq./Kg. Mean total body exchangeable sodium (TBNa) in 37 patients was 50.3 mEq./Kg., contrasted with a mean control value of 41.9 mEq./Kg. Mean extracellular fluid volume (ECF) was 232.7 c.c./Kg., contrasted with a mean value for normal subjects of 162.6 c.c./Kg.

The differences between the means for TBK, TBNa, and ECF in the group with pulmonary insufficiency and the controls were statistically significant.

Fig. 1 indicates the relationship between measurements of calculated arterial carbon-dioxide tension and TBNa. There was a significant linear correlation between these two variables. Only 4 of the 37 patients in whom TBNa was determined were considered to be in congestive failure at the time of study.

TBNa correlated poorly with calculated arterial oxygen tension and pH (Figs. 2, 3), as did TBK and ECF with the arterial blood carbon-dioxide and oxygen tension and pH (Figs. 4-9).

FIG. 2

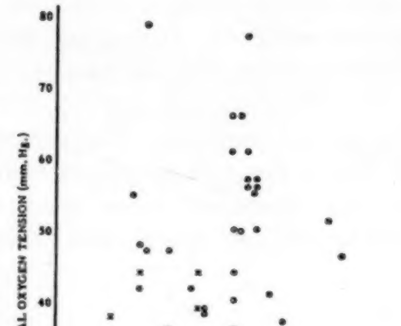

FIG. 4

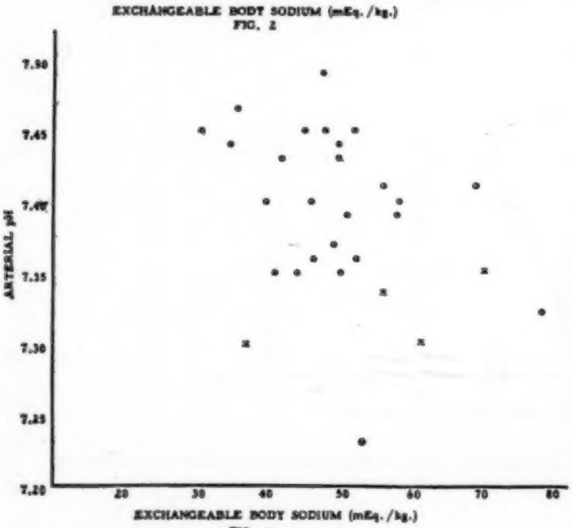

FIG. 3

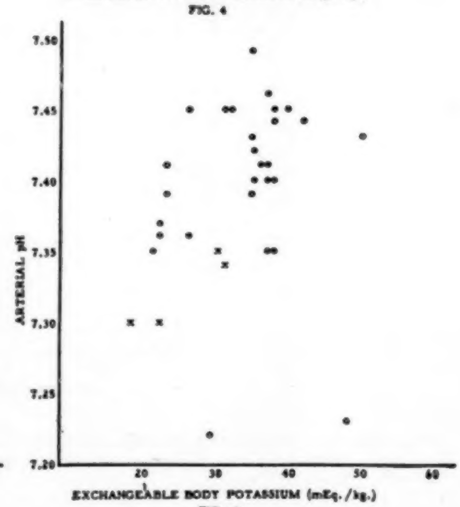

FIG. 5

Fig. 2.—Absence of linear relationship between exchangeable body sodium and arterial oxygen tension. (In Figs. 2-5, *X* indicates presence of congestive failure.)

Fig. 3.—Absence of linear relationship between exchangeable body sodium and arterial blood pH.

Fig. 4.—Absence of linear relationship between exchangeable body potassium and arterial oxygen tension.

Fig. 5.—Absence of linear relationship between exchangeable body potassium and arterial blood pH.

DISCUSSION

Significant alterations in total body exchangeable potassium, total body exchangeable sodium, and volume of extracellular fluid have been demonstrated in patients with chronic pulmonary insufficiency. These patterns have been described in a variety of chronic disease states, and have been attributed to decreased intake of food and/or increased catabolic processes.[8] Aikawa[23] demon-

strated progressive loss of potassium in rabbits during starvation. Other factors that have been incriminated are increased fat content of the body and expansion of extracellular fluid compartment as a result of edema.[8] Moore[9] has postulated a chronic state of energy deficit, often associated with depletion of potassium, slight increase in the volume of extracellular fluid, and hypertonicity of the extracellular fluid in starvation states. This is associated with leakage of sodium into the cells.

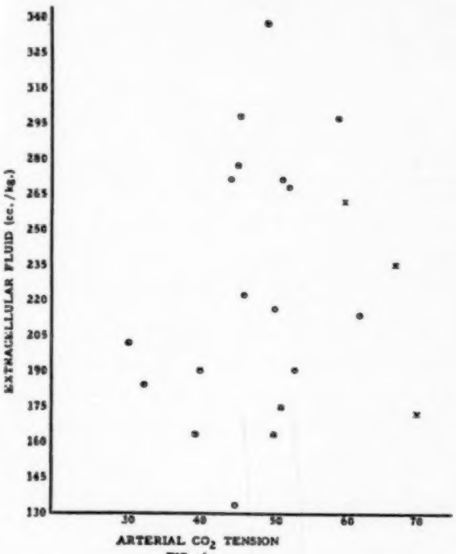

FIG. 6

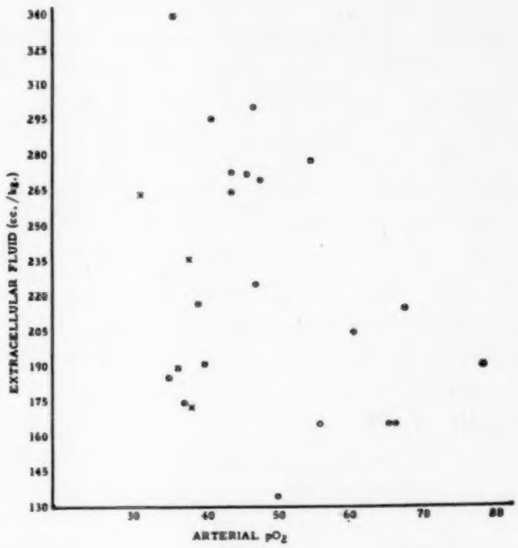

FIG. 8

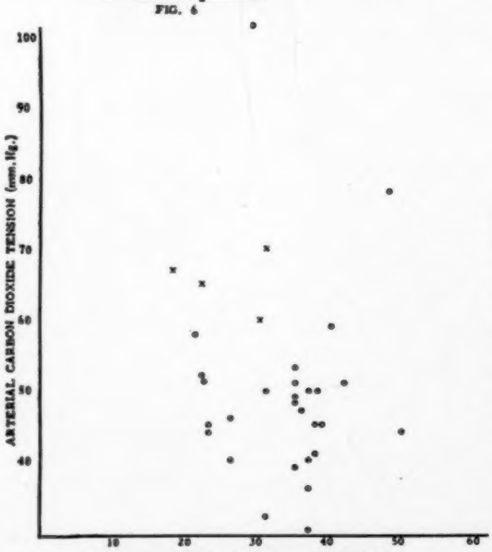

FIG. 7

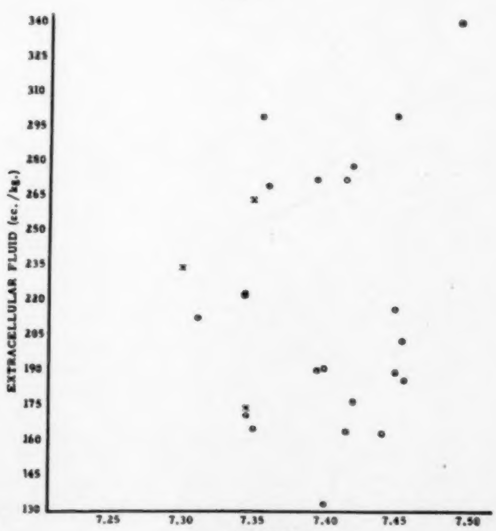

FIG. 9

Fig. 6.—Absence of linear relationship between arterial carbon-dioxide tension and extracellular fluid (radiosodium). (In Figs. 6-9, *X* indicates presence of congestive failure.)

Fig. 7.—Absence of linear relationship between exchangeable body potassium and arterial carbon-dioxide tension.

Fig. 8.—Absence of linear relationship between arterial oxygen tension and extracellular fluid (radiosodium).

Fig. 9.—Absence of linear relationship between arterial blood pH and extracellular fluid (radiosodium).

Cellular loss of potassium has also been described in respiratory acidosis[24] and in alkalosis.[25] It has been postulated that as potassium leaves the cell, sodium and hydrogen ions enter as replacements.[26] The present study indicated a poor correlation between depletion of potassium and arterial blood carbon-dioxide tension and pH. However, there was a significant linear correlation between increased arterial carbon-dioxide tension and the retention of sodium. The presence or absence of congestive failure did not influence these results. It is conceivable that the retention of sodium may be associated with the retention of carbon dioxide as part of the physiologic buffering mechanisms.

SUMMARY AND CONCLUSIONS

In a study of 42 patients with chronic pulmonary insufficiency, significant ($P < 0.01$) decrease in total body exchangeable potassium was found. Total body exchangeable sodium was studied in 37 subjects, and a significant ($P < 0.01$) retention of sodium was found. In 22 of these patients, extracellular fluid was estimated by dilution of radiosodium, and a significant ($P < 0.01$) increase was found. There was a significant ($0.02 > P > 0.01$) linear correlation between increase in exchangeable body sodium and arterial carbon-dioxide tension. No such correlation existed between the exchangeable body sodium and the calculated arterial oxygen tension. No linear correlation could be demonstrated between exchangeable body potassium and the arterial blood measurements, nor could any such correlation be made for extracellular fluid.

The authors are indebted to Catherine Osgood, B.S., Ruth Scheer, B.A., and Albert Johnson, Sc.B., for their technical assistance, and to Iris Kiem, M.S., M.P.H., for her invaluable biostatistical analyses.

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Experimental and Laboratory Reports

Atrial Fibrillation as a Self-Sustaining Arrhythmia Independent of Focal Discharge

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All of the theories advanced to explain atrial flutter and fibrillation are variations of the circus movement and ectopic focus theories. Circus movement about an obstacle has been established experimentally by Rosenblueth and Garcia-Ramos,[1,2] and it is likely that nature sometimes performs a similar experiment. Ectopic focal activity has also been produced experimentally by Scherf,[3] and some rapid atrial mechanisms in patients may well have their genesis in unifocal or multifocal ectopic pacemakers. Since both circus movement and ectopic focus mechanisms have been produced experimentally, it is unrealistic to propose that only one of these mechanisms can exist in patients.

Both theories differentiate between flutter and fibrillation in terms of the frequency of the governing agency. Flutter is considered to be rapid enough to show continuous atrial activity in the electrocardiogram and slow enough to permit essentially uniform activation of the atria. Atrial flutter can certainly be produced by repetitive discharge from an ectopic focus at an appropriate frequency. It can also be produced, within the normal parameters of atrial conduction velocity and refractory period, by circulation of an excitation wave about an obstacle of suitable circumference. In the former case, arrest of the flutter will be expected when the ectopic pacemaker is suppressed; in the latter case the dysrhythmia will end if the circus path is interrupted.

The term "atrial fibrillation" is applied both clinically and experimentally to tachycardias so rapid that uniform atrial excitation does not occur. Because of the irregular atrial activity it becomes difficult to prove which of several possible mechanisms exists. It is conceivable that a circus movement could

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Supported by a grant from the Life Insurance Medical Research Fund.
Received for publication Feb. 4, 1959.

exist in a path in which the refractory period is briefer than in the rest of the atrium. In this situation the circuit length might be short enough to result in a frequency of impulse discharge exceeding the capacity of the atria to follow regularly. It is also conceivable that an ectopic pacemaker could fire at a frequency taxing the properties of the surrounding atrial muscle. It is, however, difficult to believe that either of these mechanisms would be endowed with sufficient stability to persist for years as fibrillation often does.

Fibrillation may be started by a rapidly discharging focus or even by a single premature systole. The initiating agency may be a stimulus from electrodes, a rapidly discharging aconitine focus, a spontaneous premature beat, or a circus movement whirling about an obstacle. Whatever the initiating mechanism, fibrillation may persist after that mechanism ceases to operate. It becomes necessary then to consider this arrhythmia as a stable state compatible with the normal parameters of atrial behavior but independent of its progenitor, whether this be a circus path or an ectopic focus. Neither of the current theories provides a satisfactory explanation of this phenomenon. The necessity for an alternative explanation for "true" (independent and self-sustaining) fibrillation as contrasted to simple rapid and irregular atrial excitation is apparent.

It is the purpose of this report to present evidence that fibrillation can exist as a stable state, self-sustained and independent of its initiating agency, and to present a hypothesis which explains these and other features of fibrillation.

METHODS

Dogs of both sexes, weighing from 6 to 20 kilograms and anesthetized with pentobarbital, 30 mg./Kg., or thiopental, 20 mg./Kg., followed by barbital, 200 mg./Kg., were used in all experiments. Under artificial respiration the heart was exposed through a mid-sternal incision and cradled in the opened pericardium. Both vagi were cut in the neck, and stimulating electrodes were applied to the right nerve below the point of section. Stimulating electrodes and one or more pairs of recording electrodes were attached to the surface of the right atrium, and recording electrodes were applied to the surface of the right ventricle. Responses were recorded on a Grass ink-writing polygraph.

Atrial dysrhythmias were produced by repetitive stimulation of the right atrium, or by application of aconitine in concentrations of 1:2000 to 1:500, usually by injection of 0.01 to 0.03 c.c. into the atrial muscle near the tip of the right appendage. On occasion the site of aconitine injection was blocked off by application of a rubber-shod intestinal clamp across the base of the appendage.

RESULTS

Response of Atrium to Electrical Stimulation.—According to the unitary hypothesis, it is implied that flutter differs from fibrillation only in the frequency of one or more ectopic foci and the degree of regularity of the atrial response. Experiments were performed to determine the frequency at which flutter, as defined in these terms, merged into fibrillation. Through electrodes attached to the tip of the right atrial appendage, driving stimuli were applied at frequencies increasing gradually from about 4 per second up to 20 per second. Since vagal stimulation is known to increase the likelihood of fibrillation during rapid excitation of the atria, responses were recorded with and without excitation of the right vagus at various frequencies.

In the absence of vagal stimulation the atrium followed driving frequencies up to 6 or 7 per second without intermission and without irregularities of the electrical responses. At slightly higher frequencies electrical alternation often appeared, but so long as the atria followed the driving stimulator regularly, cessation of stimulation was promptly followed by resumption of the sinus rhythm. At frequencies of 9 to 11 per second, at a sharply demarcated point in time, the atrial electrical responses became grossly irregular (Fig. 1,*A*). Beyond this point the atrial arrhythmia often persisted for a few seconds after cessation of stimulation.

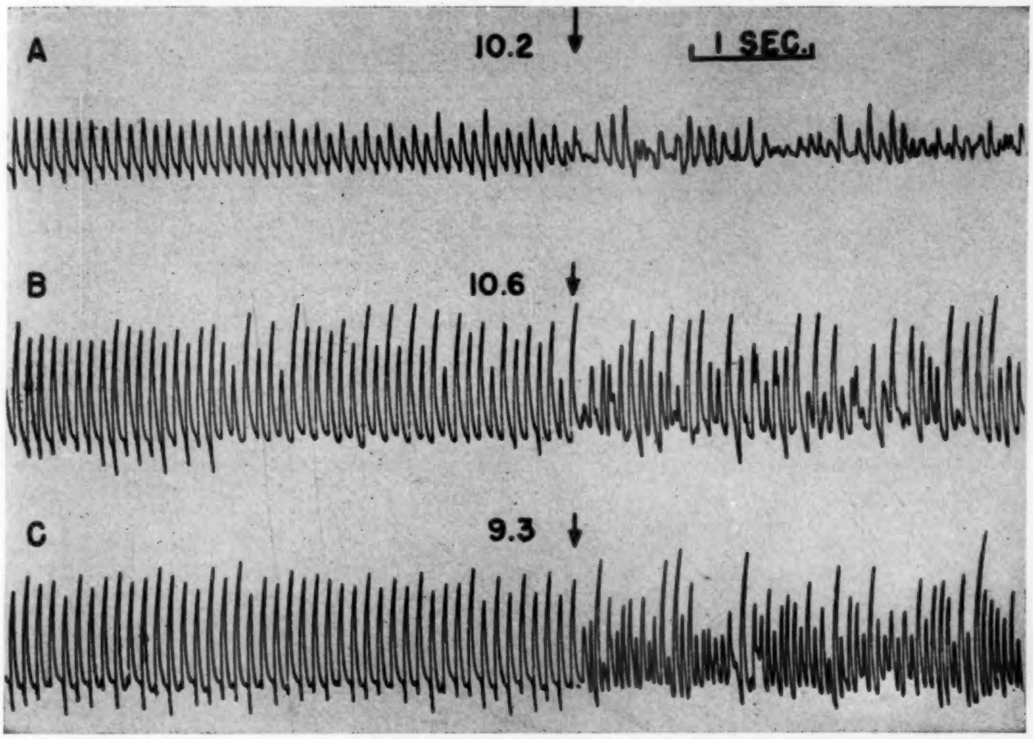

Fig. 1.—Dog weighing 15 kilograms and anesthetized with pentobarbital. Vagi cut. Records of electrical activity of right atrial appendix during gradual acceleration. *A*, Without vagal stimulation. *B*, During stimulation of right vagus at 5 cycles per second (sufficient to reduce spontaneous sinus frequency from 198 to 111 per minute). *C*, During vagal stimulation at 10 cycles per second (sinus frequency reduced from 198 to 69 per minute). Arrows indicate point at which atria fail to follow stimulus frequency regularly. Figures indicate driving frequency during 1 second just preceding irregular atrial responses. Time calibration is shown at right of upper record.

Although it might be expected that vagal stimulation, by abbreviating the atrial refractory period, would permit the atria to follow the stimulator regularly to higher frequencies, it was found that the point at which the atrial electrical responses showed alternation of configuration, and the point at which complete degeneration of the responses occurred, were almost precisely the same during vagal stimulation as during control observations (Fig. 1,*B* and *C*). In fact, if the atria were accelerated rapidly, fibrillation occurred at lower frequencies dur-

ing vagal stimulation. As in control observations, the normal sinus rhythm was immediately resumed if the stimulator was turned off while responses were still regular in rhythm. If stimulation was carried beyond the point at which the responses became irregular, the arrhythmia persisted after cessation of atrial stimulation as long as vagal stimulation was maintained, and ceased within seconds when vagal stimulation was discontinued.

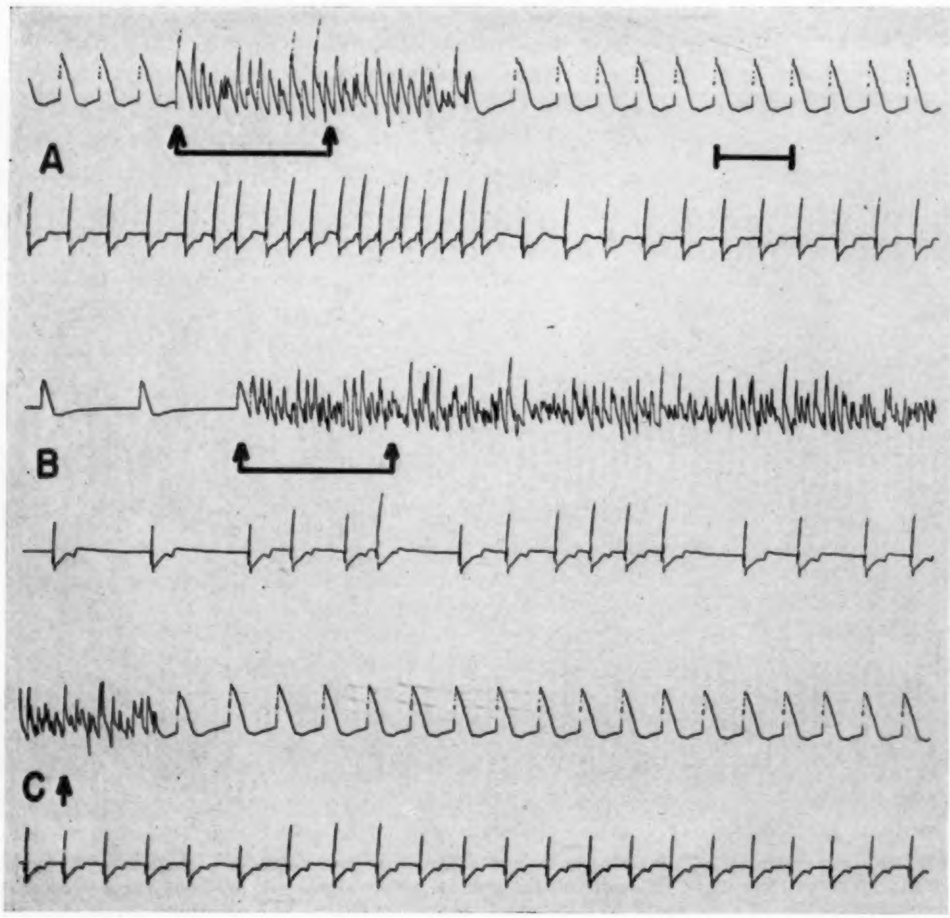

Fig. 2.—Dog weighing 9.8 kilograms and anesthetized with pentobarbital. Vagi cut. Upper record, atrial electrogram; lower record, ventricular electrogram. Time calibration at right of part *A* is 1 second. *A*, Without vagal stimulation; atrial stimulation at 20 cycles per second between arrows. *B*, During right vagal stimulation; atrial stimulation at 20 cycles per second between arrows. Between *B* and *C*, 12 seconds elapsed. At arrow in *C*, vagal stimulation stopped.

In other experiments the dependence of sustained fibrillation upon cholinergic stimulation was tested by subjecting the atria to brief periods of stimulation at a frequency of 20 per second, with and without simultaneous excitation of the right vagus nerve. Fibrillation, as defined by rapid and irregular electrical activity in the atria, rarely outlasted the atrial stimulation by more than a few seconds in the absence of vagal stimulation, but always persisted for the

duration of vagal stimulation if the latter was sufficiently intense. Fig. 2 illustrates such an experiment. In part *A*, without vagal stimulation, electrical stimulation of the atrium at 20 per second was applied for 2 seconds, as indicated by the arrows. The irregularity persisted for less than 2 seconds after atrial stimulation was discontinued. In Fig. 2,*B*, atrial stimulation was applied for 2 seconds during vagal stimulation strong enough to slow the sinus frequency by slightly more than 50 per cent. Fibrillation persisted until vagal stimulation was stopped (at the arrow in Fig. 2,*C*), about 20 seconds later.

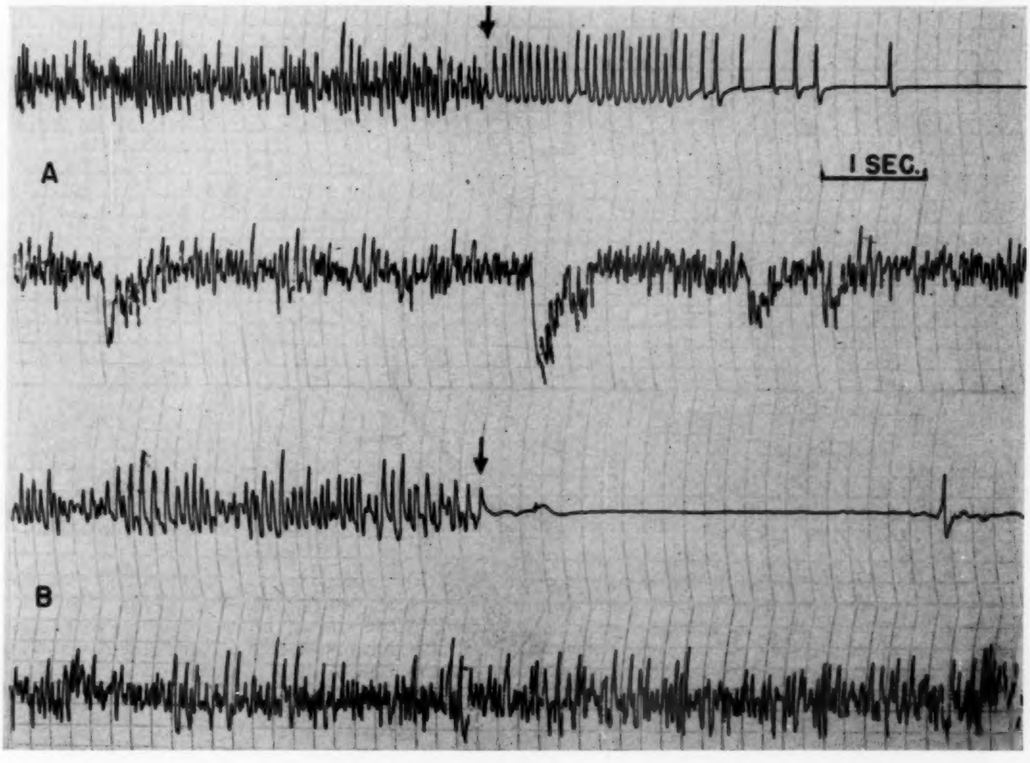

Fig. 3.—Dog weighing 15 kilograms and anesthetized with pentobarbital. Vagi cut. Upper tracing, electrogram taken near tip of right atrial appendage; lower tracing, from body of right atrium. Fibrillation was induced by a brief period of stimulation at the tip of the auricle during vagal stimulation. At arrow in *A*, the clamp was applied with moderate pressure across the base of the auricle. At arrow in *B*, the clamp was applied with crushing force during the second episode of fibrillation.

By all criteria of direct observation and of the electrical records of atrial and ventricular activity, the arrhythmia produced by rapid atrial excitation during vagal stimulation was fibrillation, and it persisted after the precipitating focus (the stimulator) was turned off. It was considered remotely possible, however, that rapid electrical excitation of the atrium created an ectopic focus which continued to fire from the site of stimulation after the driving stimulator was stopped. If this were the case, it would be expected that application of a clamp across the base of the atrial appendage should result in arrest of fibrillation in the body of the atrium, and persistence of rapid activity in the isolated

appendage. Accordingly, recording electrodes were attached to the atrial appendage near the stimulating electrodes and to the body of the right atrium near the superior vena cava. After fibrillation was established by a brief period of rapid atrial stimulation during strong vagal stimulation, a clamp was applied to the base of the auricle. When the clamp was closed with moderate pressure,

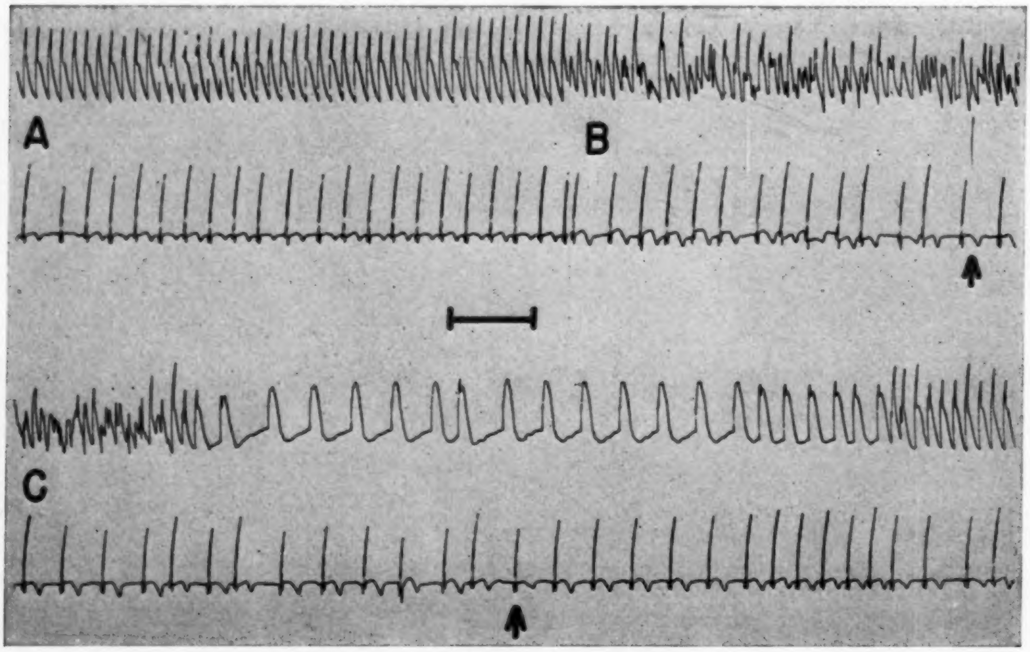

Fig. 4.—Dog weighing 15 kilograms and anesthetized with pentobarbital. Vagi cut. Upper tracing, electrogram taken from body of right atrium; lower tracing, ventricular electrogram. *A*, Flutter recorded 30 seconds after intramural injection of 0.02 c.c. of 1:500 solution of aconitine near tip of auricular appendage. *B*, One minute later, fibrillation. Application of the clamp across the base of the auricle (arrow in *B*) was followed within 3 seconds by resumption of sinus rhythm (in record *C*, which is continuous with *B*). Release of the clamp (at arrow in *C*) was followed by resumption of ectopic rhythm. Time calibration is 1 second.

fibrillation continued in the body of the atrium, but was replaced by a tachycardia decelerating within a few seconds to complete inactivity in the auricular appendage (Fig. 3,*A*). When the clamp was applied abruptly and with crushing force, activity in the appendage ceased promptly (Fig. 3,*B*) while fibrillation continued unchanged in the rest of the atrium. On other occasions the clamp was applied during rapid stimulation of the auricular apex; fibrillation continued on both sides of the clamp as long as atrial stimulation was continued, but stopped in the clamped-off appendage as soon as the stimuli were cut off. On the other hand, if the clamp was similarly applied and vagal stimulation was then stopped, fibrillation stopped promptly in the body of the atrium but continued in the auricle until the driving stimulator was turned off.

Response of the Atrium to Aconitine.—Injection of small volumes of aconitine solution in low concentration into the atrial muscle near the tip of the appendix resulted in atrial tachycardia at 5 to 8 per second. At these "flutter" frequencies,

as with electrical stimulation in the same range, the electrical responses of the atrium were regular and uniform; vagal stimulation did not alter atrial behavior. Application of the clamp at the base of the auricle resulted in immediate resumption of sinus rhythm in the body of the atrium while the tachycardia persisted in the auricle, whether or not the vagus was stimulated.

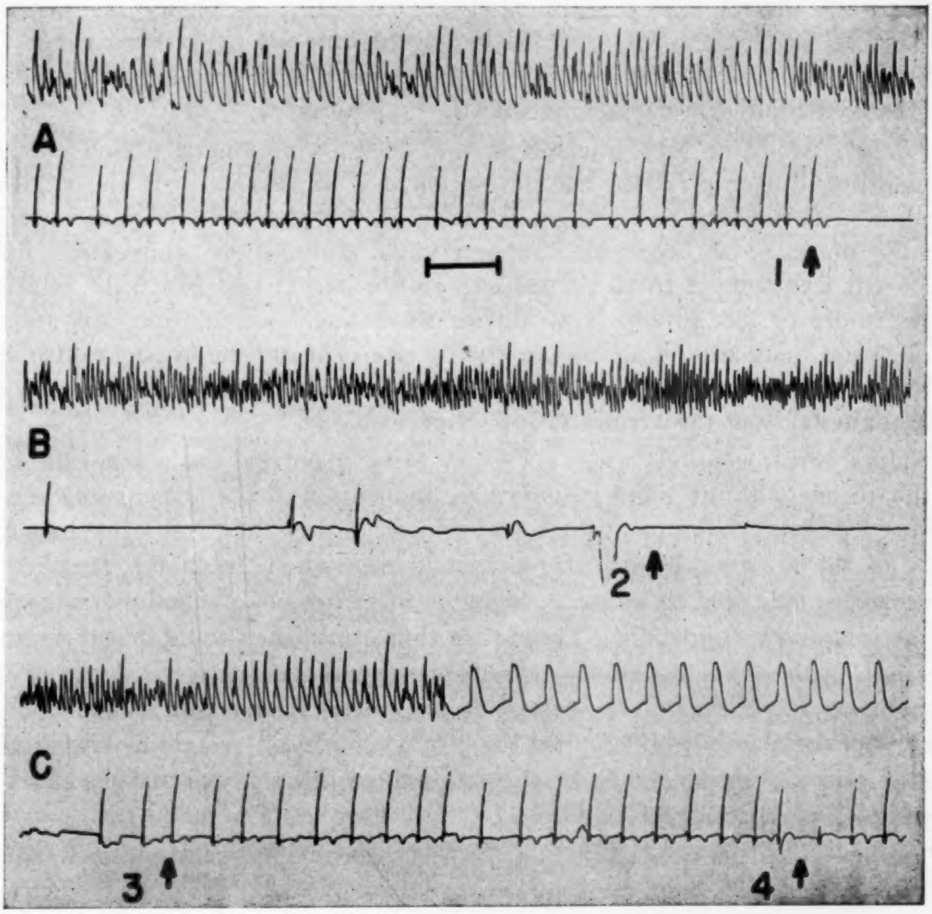

Fig. 5.—Same experiment as in Fig. 4; 2½ minutes after the injection of aconitine. At *1*, vagal stimulation is begun; at *2*, the clamp is applied across the base of the auricle. Lapse of 24 seconds between *B* and *C*. At *3*, vagal stimulation is stopped. At *4*, clamp is removed. Time calibration is 1 second.

After higher doses of aconitine, frank fibrillation developed, with characteristically rapid and irregular atrial activity. When the auricular clamp was applied without vagal stimulation, fibrillation was promptly replaced by sinus rhythm in the body of the atrium (Fig. 4). Even in the clamped-off auricle fibrillation was usually replaced by more regular patterns of tachycardia after clamping.

During vagal stimulation, application of the clamp never resulted in cessation of fibrillation in the body of the atrium. Fig. 5 illustrates this phenomenon.

In part *A*, vagal stimulation was begun at the first arrow during a period of rapid and irregular tachycardia induced by the injection of aconitine. At the second arrow (part *B*) the clamp was applied firmly across the base of the auricle. Fibrillation continued in the body of the atrium for about 30 seconds, and stopped only when vagal stimulation was discontinued (third arrow, part *C*). Removal of the clamp (at arrow 4) was followed within 25 seconds by resumption of fibrillation. The site injected with aconitine reacted in essentially the same manner as the electrical focus: fibrillation, once induced by either agency, was self-perpetuating in the body of the atrium as long as the vagus was stimulated, and was self-limited in the absence of vagal discharge.

When aconitine was injected in low doses, a prolonged period of slowly accelerating flutter preceded the development of fibrillation. If the vagi were stimulated during this early stage, the frequency of the atrial responses was not usually altered. On occasion, however, vagal stimulation "converted" flutter (apparent frequency 8 to 10 per second) to fibrillation (see Fig. 5,*A*), which reverted more or less promptly to flutter when vagal stimulation was stopped. Application of recording electrodes to the site of aconitine application in such instances revealed that the focus itself was discharging at a frequency double that of the body of the atrium (16 to 20 per second).

On several occasions when a rapidly firing aconitine focus was established in the auricle without vagal stimulation, application of the auricular clamp was followed by conversion of fibrillation to flutter rather than sinus rhythm in the body of the atrium. The flutter persisted even when the clamp pressure was increased sufficiently to cause permanent interruption of conduction between the atrium and its appendix. The flutter thus established could be captured and arrested, in the same manner as a circus movement flutter, by decelerating atrial stimulation starting at a rate exceeding the flutter frequency. It is likely that the site of the clamp itself supplied the obstacle for a self-sustaining circuit which then persisted independently of the original aconitine focus, as in the experiments of Brown and Acheson.[4]

When aconitine was applied on the atrial surface by means of small squares of filter paper soaked in the solution, atrial tachycardia developed much more gradually than following the injection of discretely localized doses. Once established, both flutter and fibrillation often failed to yield to application of the auricular clamp. It was likely that the aconitine in these instances had spread extensively from the site of application, so that clamping no longer separated the body of the atrium from all loci of action of the alkaloid. This probability was supported by the observation that acetylcholine similarly applied at the tip of the auricle caused prompt and profound slowing of the sinus node.

DISCUSSION

In the experiments described above, atrial flutter induced either by electrical stimulation or by injection of aconitine was abolished when the inciting agency was eliminated; atrial fibrillation, as judged by gross irregularity of the

atrial electrograms, could persist independently of the inciting agency; and independent survival of fibrillation was possible only in the presence of adequate cholinergic discharge.

When an impulse is initiated in fully excitable atrial muscle, it may be expected to propagate rapidly and uniformly in all directions from the site of origin. Recovery from such a primary activation, while following roughly the same concentric pattern of spread, does not, however, progress so uniformly; i.e., the refractory state does not have precisely the same duration in all atrial fibers.[5] It follows that the "spread" of recovery will have a serrated configuration: some fibers will be excitable at a time when closely adjacent fibers on either side are still refractory. Since conduction velocity is low in relatively refractory tissue, it follows that a second response initiated at the site of origin of the primary response will be irregularly propagated: it will rapidly invade those fibers in an advanced state of recovery and it will be retarded or altogether stopped by those fibers which are still partially or totally refractory. In other words, the advancing wave front of the second response must tend to conform itself to the retreating edge of the preceding response, and must also become serrated in contour. If this process is repeated a second or a third time, temporal dispersion of the processes of excitation and of recovery must become accordingly greater. One fibril may become activated while its nearest neighbor repolarizes; even the frequencies of individual elements, at least over a brief span of time, may be widely variant. Orderly spread of excitation will no longer be possible; the grossly irregular wave front becomes fractionated as it divides about islets or strands of refractory tissue, and each of the daughter wavelets may now be considered as independent offspring. Such a wavelet may accelerate or decelerate as it encounters tissue in a more or less advanced state of recovery. It may become extinguished as it encounters refractory tissue; it may divide again or combine with a neighbor; it may be expected to fluctuate in size and change in direction. Its course, though determined by the excitability or refractoriness of surrounding tissue, would appear to be as random as Brownian motion. Fully developed fibrillation would then be a state in which many such randomly wandering wavelets coexist.

The likelihood of persistence of this process should depend upon the number of wavelets present. If the number is large, there is little chance that all elements will fall into phase (i.e., be refractory or excitable simultaneously), but if the number is small there is a considerable probability that they may fuse and permit resumption of a sinus rhythm. The average number, in turn, will depend upon (1) the atrial mass, (2) the mean duration of the refractory period, and (3) the mean conduction velocity. Obviously, a larger mass of tissue can support a larger total number of independent wavelets. It is also obvious that a brief refractory period will allow a larger total number of coexisting wavelets than a long one. If the refractory period were sufficiently prolonged, the total atrial mass would soon be left in a refractory state; i.e., all wavelets would merge and fibrillation would cease. That conduction velocity must be a factor is also apparent, for if every impulse were rapidly propagated to the remotest extremity

of the atrium, fractionation and total disorganization of atrial behavior would not occur.

Emphasis on the importance of these factors recurs in many discussions of the mechanism of fibrillation. Garrey[6] demonstrated that fibrillation stopped promptly when the mass of the tissue was reduced sufficiently by cutting, and it has been stated by Martinez[7] that fibrillation cannot be sustained in less than 1 gram of cardiac tissue. Garrey, emphasizing also the importance of the shape of the tissue, showed that fibrillation cannot pass a narrow isthmus.

The importance of abbreviation of the refractory period has been recognized by almost all investigators. Mines[8] considered the role of progressive shortening with induced acceleration; Rothberger and Winterberg[9] assigned the effects of vagal stimulation and of vagomimetic drugs to their action upon the atrial refractory period; Burn and associates[10,11] have recently emphasized the importance of cholinergic mechanisms in the genesis of sustained atrial fibrillation; and Holland and co-workers[12] have shown that fibrillation may be maintained in isolated rabbit atria exposed to depletion of potassium and acetylcholine, both of which reduce the refractory period.

The significance of depression of conduction velocity is recognized in all discussions of fibrillation which implicate propagation of impulses in the relatively refractory period, and was specifically considered by Moe, Harris and Wiggers[13] and by Moe and Mendez[14] as a factor in the induction of ventricular fibrillation.

Recognition of the importance of nonuniformity of these several attributes of myocardial behavior dates from Engelmann[15] and has been repeated by Mines,[8] Garrey,[6] Rosenblueth and Garcia-Ramos,[1,2] Wiggers,[16] Alessi and associates,[5] and Brooks and associates.[17]

In all these studies it is stated, assumed, or implied that fibrillation results from fractionation of early premature responses initiated in partially and irregularly excitable tissue. Responses initiated repetitively in partially refractory tissue will, when fractionated into small wavelets, yield rapid irregular activity, i.e., fibrillation. Whether the fibrillation will be self-sustaining is then a function of the combination of properties (mass, refractory period, conduction velocity) which exist or are induced in the tissue. Those factors which increase the degree of fractionation will increase the mean number of wavelets which may wander independently in the atria, and will correspondingly reduce the likelihood of spontaneous arrest (falling into phase). Large mass, short refractory period, and slow conduction will all favor perpetuation of the arrhythmia by permitting the coexistence of many independent, randomly wandering wavelets. The results of the present study may be interpreted in terms of this multiple wavelet hypothesis.

Stimulation of the atria at frequencies accelerating up to about 10 per second did not cause disorganization of atrial activity, while higher frequencies caused the irregular electrical responses characteristic of fibrillation. It may be assumed that the refractory period of *all* atrial cells was reduced to about 0.1 second by acceleration, but that the refractory period of some cells could not be further shortened. Intermittency and irregularity of the gross electrical behavior was,

of course, the inevitable result when frequencies above 10 per second were imposed. It is perhaps surprising that vagal stimulation failed to increase the maximum frequency which the atria could follow. It has been demonstrated recently, however, that the refractory period of some atrial fibers is almost unaffected by vagal stimulation.[5] Since the upper frequency limit of regular response must be imposed by those fibers which have the longest refractory period, it becomes apparent that vagal stimulation cannot increase this limiting frequency. It is also apparent, since vagal stimulation causes marked shortening of the refractory period of some fibers, that fractionation of the wave front (and degeneration into independent wavelets) of an early premature response, and resultant fibrillation, is much more likely to occur during vagal stimulation. In fact, a single premature response initiated at a site subject to profound vagal influence often results in fibrillation, as reported by Alessi and associates.[5]

Self-sustained fibrillation always resulted when the atria were stimulated briefly at high frequency during adequate vagal excitation, but never when the vagi were at rest. In terms of the multiple wavelet hypothesis it appears that vagal stimulation, in addition to facilitating the initial fractionation of responses, reduces the *mean* refractory period of atrial cells, and thereby increases the total possible number of wandering wavelets.

In the absence of vagal stimulation, fibrillation could not sustain itself for more than a few seconds, suggesting that the limited number of wavelets that can be supported by the atria of the average dog is too small to prevent chance fusion and obliteration of the arrhythmia.

The importance of atrial mass and refractory period, implied above, is well illustrated by the experiments in which a clamp was applied across the base of the auricle during fibrillation sustained by vagal stimulation. Fibrillation persisted in the body of the atria, but stopped abruptly in the appendix. It was implied by Garrey,[6] who performed similar experiments, that the mass of the isolated appendix was too small to support circus pathways of adequate dimension; in terms of the rather closely related wavelet hypothesis, it may be assumed that the mass of tissue remaining in the isolated auricle contained too few wavelets to permit a self-sustained arrhythmia, while the much larger mass of the body of the atrium supported an adequate number. Proponents of the ectopic focus hypothesis might object that the focus was not in the appendix, or that anoxia was produced in the tissue beyond the clamp, or that vagal influence (as a source of ectopic foci) was interrupted by the clamp. These possible objections, however, are of doubtful validity, for the appendix was the site of the stimulation which initiated the arrhythmia; anoxia could not have developed in the fraction of a second which elapsed between application of the clamp and arrest of fibrillation; and application of the clamp should have briefly stimulated those vagal fibers which passed through the crushed area.

The experiments with aconitine are in every respect analogous to those with electrical stimulation. So long as the acontine focus discharged at a frequency of less than 9 or 10 per second, vagal stimulation failed to alter atrial behavior, and isolation of the aconitine focus by clamping resulted in resumption of sinus rhythm in the body of the atria. When the aconitine focus discharged

more rapidly, application of the clamp still abolished the arrhythmia in the atrium; but when the vagi were stimulated, fibrillation persisted on both sides of the clamp.

The results reported above are not consistent with a unitary hypothesis of atrial arrhythmias; neither are they consistent with a circus movement hypothesis in the sense commonly attributed to Lewis. They can be explained in terms of a wavelet hypothesis which has its origin in the observations of Garrey, anteceding both of the current controversial theories. They emphasize the necessity of a definition of fibrillation in terms of *mechanism* rather than in terms of the gross and superficial criterion of irregularity of electrical events in the atria. We may conclude that irregular activation of the atria may be produced by (1) a single rapidly discharging ectopic focus, whether electrically or chemically induced, (2) multiple rapidly discharging foci, or (3) a rapidly circulating circus movement (transit time less than 0.1 second, under the conditions of the present experiments). We may further conclude that true fibrillation may be self-sustained and independent of whatever initiating agency, provided the atria are large enough (as the adult human atria probably are) or have a sufficiently brief refractory period. It is conceivable that all possible mechanisms are encountered in the clinic.

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A Universal System of Electrode Placement for Electrocardiography and Spatial Vectorcardiography

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A comparison has been made recently[1] between the usual twelve-lead clinical electrocardiogram and a mosaic of thirteen leads derived from three orthogonal leads designed to have relatively uniform lead fields.[2,3] It was found that the latter effectively depicted the total electrical activity of the heart, but that the precordial leads of the usual clinical electrocardiogram, or, in some cases, supplementary exploratory precordial leads, were more efficient in demonstrating certain fine details of the QRS complex which are of aid in the diagnosis of myocardial infarction. It seemed desirable, therefore, to devise a system of electrode placement which would be universally applicable for obtaining the spatial vectorcardiogram (or its scalar derivatives) as well as for recording the more minute details of the electromotive forces generated by the heart.

Consideration of this problem at once suggested the seven-electrode placement advocated by Frank[4] for obtaining orthogonal vectorcardiographic leads. An objection to Frank's system is that the electrode located at point M over the spinal column requires manipulation of the subject in a manner not always desirable in severely ill patients. Therefore, it seemed preferable to eliminate this electrode. The remaining chest electrodes, located at that transverse level where the fifth intercostal space intersects the parasternal lines, are placed as follows: Electrodes A and I are located at the intersection of this transverse level with the left and right midaxillary lines, respectively. Electrode E is placed on the center of the sternum at this same level, and electrode C is located midway between points E and A, as determined by approximate linear measurement over the body surface. Although the use of a protractor for locating electrode C has been suggested,[4] such accuracy seems entirely superfluous. Electrode N is located on the left anterior side of the neck at the level of the angle of the jaw. This placement varies from the location on the posterior aspect of the neck recommended by Frank,[4] but it has the merit of convenience, especially if a suction electrode is used. Electrode F is applied to the left leg. Thus, six electrodes may be rapidly and accurately placed and need not be altered to record all of the leads to be described.

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This work was supported in part by a grant-in-aid from the American Heart Association.

Received for publication Feb. 24, 1959.

Various groups of leads may be obtained with these six electrodes. One such group consists of fourteen leads recorded in the transverse plane from electrodes A, C, E, and I. These are listed under *Transverse Leads* in Table I, and their lead vectors for Frank's[5] dipole location 22 are illustrated in Fig. 1, in which they are separated into two sets which cluster predominantly about point E (left-hand panel) and point A (right-hand panel). (Leads 1 [E-A] and 5 [C-I], common to each set, are included in each panel to illustrate the directional sequence of the leads.) The leads in the left- and right-hand panels might be considered to represent predominantly right and left ventricular leads, respectively.

TABLE I

LEAD DESIGNATIONS	ELECTRODE FORMATION OF LEAD
Transverse Leads	
1	E − A
2r	E − (.5A + .5I)
2l	(.5C + .5E) − A
3r	E − I
3l	C − A
4r	(.5C + .5E) − I
4l	C − (.5A + .5I)
5	C − I
6r	C − (.5E + .5I)
6l	(.5A + .5C) − I
7r	C − E
7l	A − I
8r	(.5A + .5C) − E
8l	A − (.5E + .5I)
Transverse' Leads	
1'	(.5E + .5N) − (.5A + .5F)
2r'	(.5E + .5N) − (.25A + .25I + .5F)
2l'	(.25C + .25E + .5N) − (.5A + .5F)
3r'	(.5E + .5N) − (.5I + .5F)
3l'	(.5C + .5N) − (.5A + .5F)
4r'	(.25C + .25E + .5N) − (.5I + .5F)
4l'	(.5C + .5N) − (.25A + .25I + .5F)
5'	(.5C + .5N) − (.5I + .5F)
6r'	(.5C + .5N) − (.25E + .25I + .5F)
6l'	(.25A + .25C + .5N) − (.5I + .5F)
7r'	(.5C + .5N) − (.5E + .5F)
7l'	(.5A + .5N) − (.5I + .5F)
8r'	(.25A + .25C + .5N) − (.5E + .5F)
8l'	(.5A + .5N) − (.25E + .25I + .5F)

Figs. 2 through 5 illustrate the effect on these leads of displacement of the dipole center from location 22. The magnitudes of such displacements are arbitrarily set as the corners of a 4-cm. square centered over location 22. When the dipole is displaced toward the right ventricle to Frank's[5] dipole location 04 (Fig. 2), the "right ventricular leads" increase in magnitude. When the dipole is moved toward the left ventricle to location 40 (Fig. 3), the "left ventricular leads" become predominant. When the dipole is displaced anteriorly and to the left to location 44 (Fig. 4), the leads which include electrode C in their con-

TABLE I—(CONT'D)

LEAD DESIGNATIONS	ELECTRODE FORMATION OF LEAD
Transverse, Leads	
1,	(.5E + .5F) − (.5A + .5N)
2r,	(.5E + .5F) − (.25A + .25I + .5N)
2l,	(.25C + .25E + .5F) − (.5A + .5N)
3r,	(.5E + .5F) − (.5I + .5N)
3l,	(.5C + .5F) − (.5A + .5N)
4r,	(.25C + .25E + .5F) − (.5I + .5N)
4l,	(.5C + .5F) − (.25A + .25I + .5N)
5,	(.5C + .5F) − (.5I + .5N)
6r,	(.5C + .5F) − (.25E + .25I + .5N)
6l,	(.25A + .25C + .5F) − (.5I + .5N)
7r,	(.5C + .5F) − (.5E + .5N)
7l,	(.5A + .5F) − (.5I + .5N)
8r,	(.25A + .25C + .5F) − (.5E + .5N)
8l,	(.5A + .5F) − (.25E + .25I + .5N)
Longitudinal Leads	
E″	(.5E + .5N) − F
E′	E − F
E	E − (.5F + .5N)
E,	E − N
E,,	(.5E + .5F) − N
C″	(.5C + .5N) − F
C′	C − F
C	C − (.5F + .5N)
C,	C − N
C,,	(.5C + .5F) − N
A″	(.5A + .5N) − F
A′	A − F
A	A − (.5F + .5N)
A,	A − N
A,,	(.5A + .5F) − N
I″	(.5I + .5N) − F
I′	I − F
I	I − (.5F + .5N)
I,	I − N
I,,	(.5I + .5F) − N
L	F − N
Routine Leads	
1	E − A
3r	E − I
3l	C − A
5	C − I
7r	C — E
7l	A − I
E′	E − F
E,	E − N
C′	C − F
C,	C − N
A′	A − F
A,	A − N
L	F − N
Vectorcardiographic Leads	
X	(.66A + .34C) − (.86I + .14E)
Y	F − N
Z	(.31C + .69E) − (.43A + .57I)

stituency increase markedly in magnitude. When the dipole is moved posteriorly and to the right to location 00 (Fig. 5), the leads partially formed by point I show a slight increase in relative magnitude. This change is less marked than with the other dipole migrations because point I is relatively distant from the heart. It should be noted that in the case of dipole location 22 (Fig. 1), the right and left ventricular leads with corresponding numbers are more or less parallel and of similar magnitude. With dipole displacement, coincidence of magnitude and direction of corresponding leads disappears.

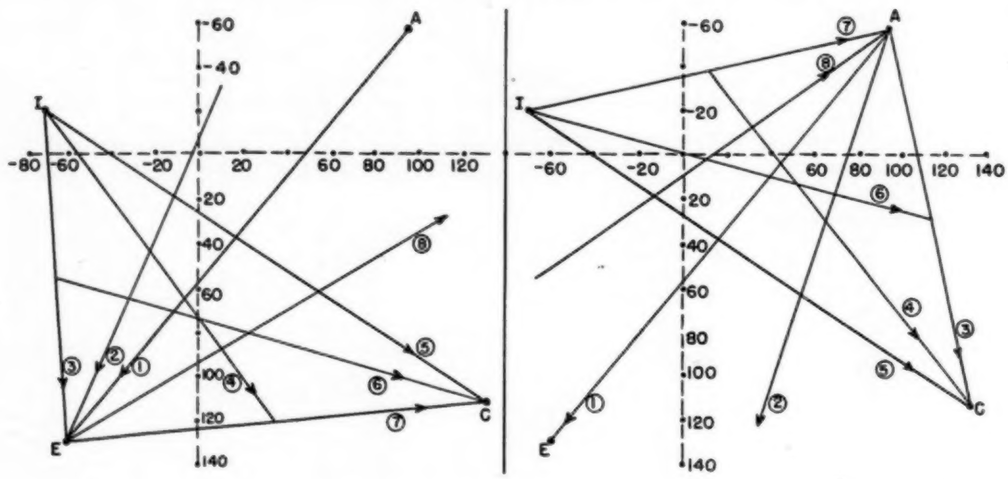

Fig. 1.—The lead vectors of the fourteen transverse leads for Frank's dipole location 22. These leads are separated into two sets which cluster about point E (left panel) and point A (right panel). The left panel illustrates the r leads and the right panel the l leads. Leads 1 and 5 are included in each panel.

Two other groups of fourteen leads are readily obtainable. One of these groups can be formed by joining electrode N with the positive poles of the fourteen transverse leads just described and also simultaneously joining electrode F with their negative poles. The positive polarities of this new group of fourteen leads are directed obliquely upward. In like manner, electrode F can be joined with the positive poles and electrode N with the negative poles of the fourteen transverse leads to form an additional group of fourteen leads, the positive polarities of which are directed obliquely downward. Like the transverse leads, these two additional groups of fourteen leads can be divided into sets of right and left ventricular leads. In effect, they can be considered to be analogous to the transverse leads but located at more superior and inferior levels, respectively. These additional leads can, therefore, be given the same numerical designations as the transverse leads, with the addition of a prime sign placed as a superscript for the more superior group and a similar sign placed as a subscript for the more inferior group. Both the superior and inferior groups are listed in Table I under *Transverse' Leads* and *Transverse, Leads*, respectively.

The six electrodes also permit the more detailed exploration of four planes which pass through the longitudinal axis of the body. Each of the four planes

is formed by electrode N, electrode F, and a third electrode located at either A, C, E, or I on the thorax, and each plane contains five separate leads and a sixth lead (F-N) which is common to all four of the planes. These twenty-one different leads are listed in Table I under *Longitudinal Leads.*

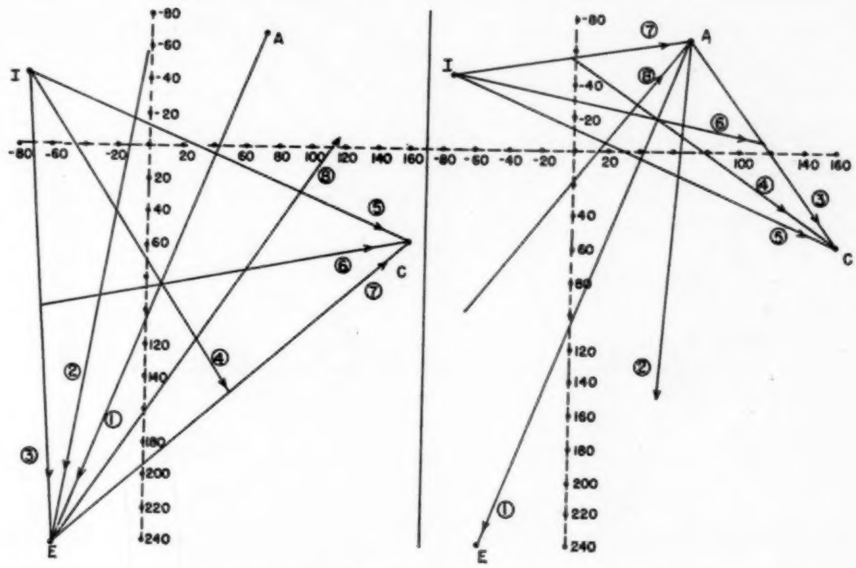

Fig. 2.—The lead vectors of the fourteen transverse leads for Frank's dipole location 04. In this illustration, as well as in Figs. 3-5, the leads are separated into r and l sets (left and right panels, respectively) as in Fig. 1.

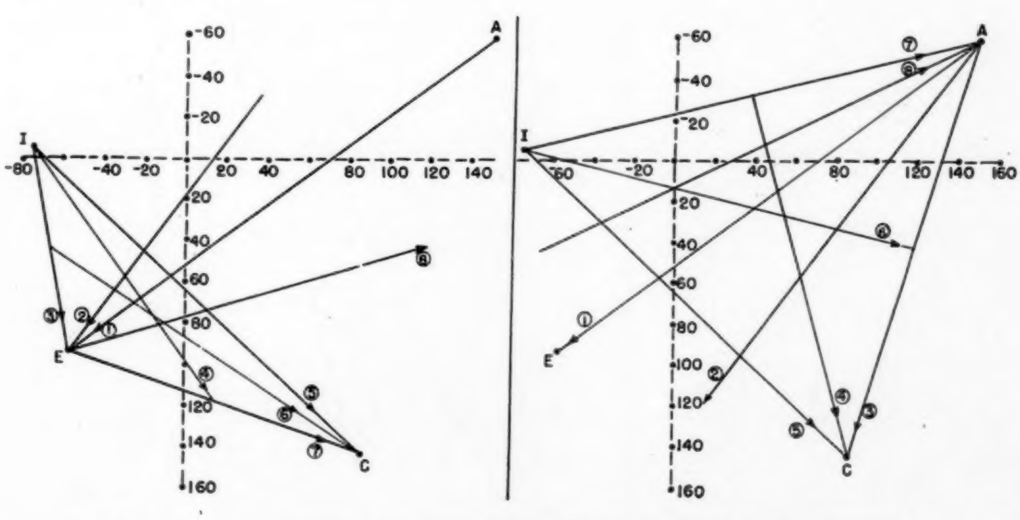

Fig. 3.—The lead vectors of the fourteen transverse leads for Frank's dipole location 40.

Under *Routine Leads* in Table I are included thirteen bipolar leads selected from the fifteen separate possible pairs of the six electrodes. Two such bipolar leads, I-F and I-N, are omitted from this list because point I is located so close to the axis of lead F-N in image space that these two leads would not, in most

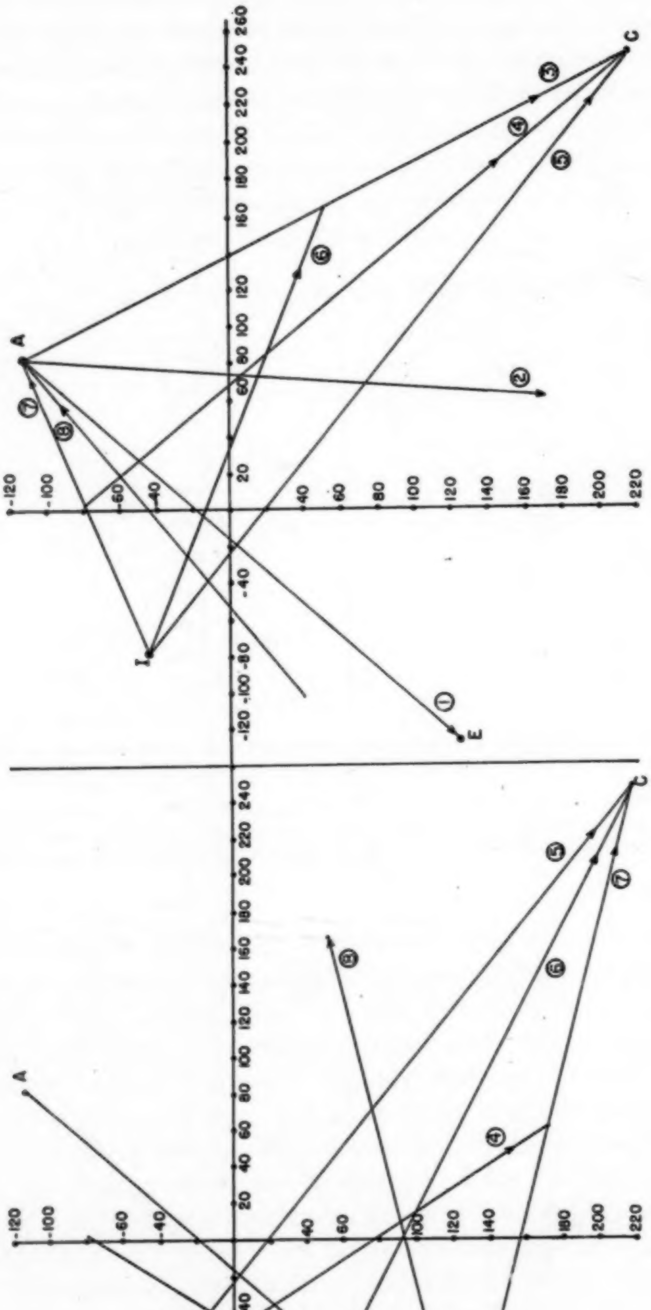

Fig. 4.—The lead vectors of the fourteen transverse leads for Frank's dipole location 44.

instances, provide any information not obtainable with lead F-N. The thirteen routine leads then consist of a small group of leads which explore the various portions of the cardiac electrical field from a variety of vantage points. Moreover, they are bipolar and, unlike "unipolar" or network leads, can be recorded without resistors in the lead circuit. Difficulty with alternating current interference is thus reduced.

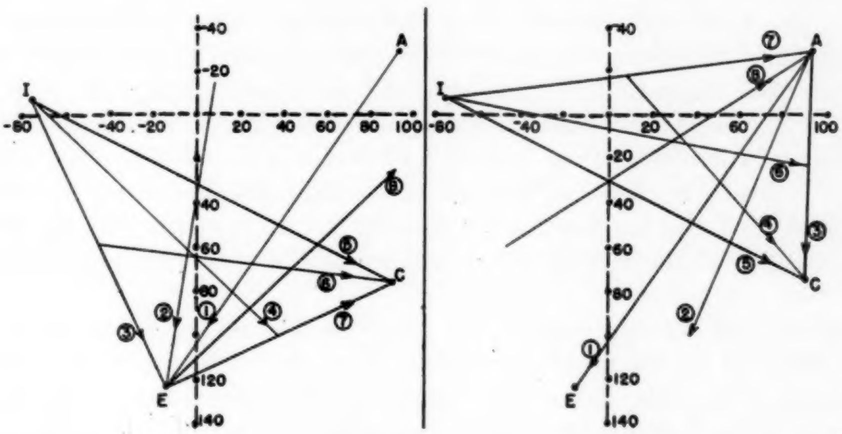

Fig. 5.—The lead vectors of the fourteen transverse leads for Frank's dipole location 00.

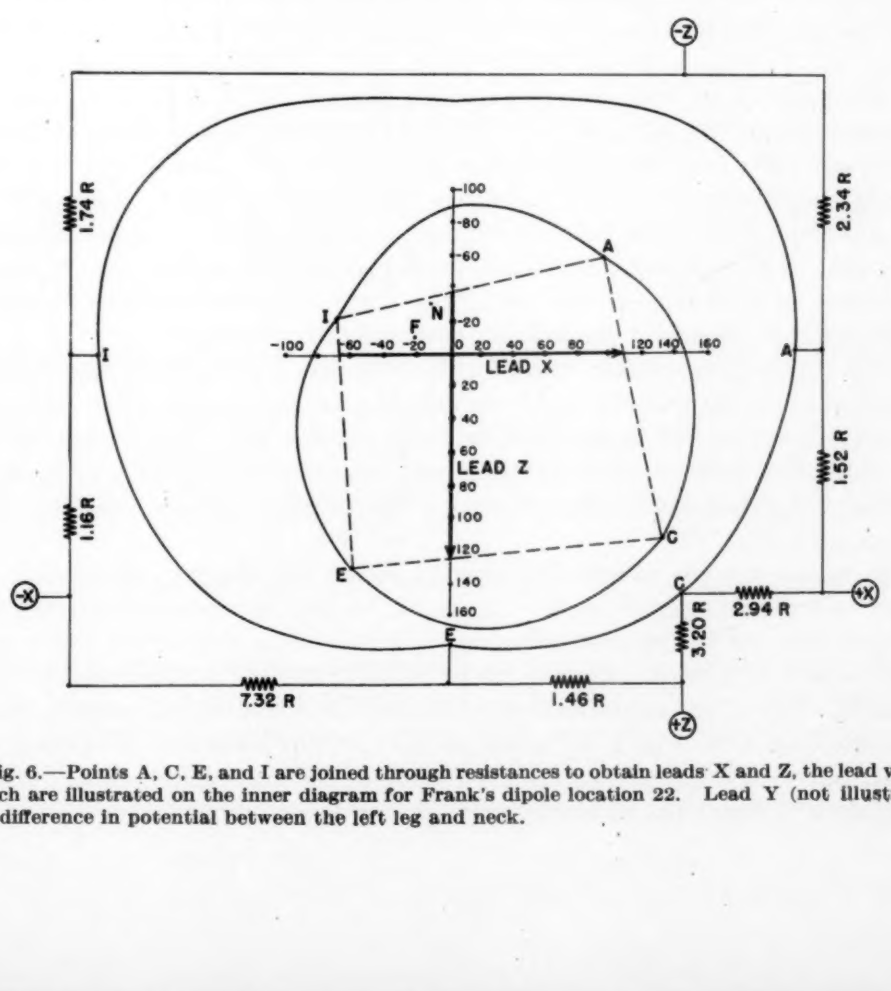

Fig. 6.—Points A, C, E, and I are joined through resistances to obtain leads X and Z, the lead vectors of which are illustrated on the inner diagram for Frank's dipole location 22. Lead Y (not illustrated) is the difference in potential between the left leg and neck.

Leads designed for obtaining vectorcardiograms are listed under *Vectorcardiographic Leads* in Table I. A diagram of leads X and Z is shown in Fig. 6. These are network leads obtained by joining the four transverse electrodes in various combinations through suitable resistances. For dipole location 22, leads X and Z have magnitudes of 176 and 161 Frank units,[5] respectively. The magnitude of lead Y between the neck and left leg is 176 units,[6] and the magnitude of its y component is 175 units.[6] In view of the fact that the dipole center of the heart is not fixed and, likewise, that body configuration varies rather widely, it seems quite superfluous to apply shunt resistances to leads X and Y in order to reduce their magnitudes to that of lead Z for dipole location 22. Fig. 7 illustrates the lead vectors of leads X and Z not only for dipole location 22 but also for dipole locations 04, 40, 44, and 00. The relative uniformity of these five lead vectors, a desirable characteristic for vectorcardiographic recording, should be contrasted with the marked fluctuations of the magnitudes and the directions of the vectors of the electrocardiographic leads when dipole migration occurs (Figs. 1-5).

Fig. 8 is the wiring diagram, and Fig. 9 shows the face panel of a switching circuit designed for the rapid recording of all of the leads discussed. The terminals shown on the upper side of each illustration are attached to the six electrodes. When the vectorcardiographic leads are recorded, the patient ground is connected to the right leg or to either arm. For the electrocardiographic leads the use of this ground connection is obviated by having one of the six electrodes which does not enter into the formation of the lead being recorded serve as the ground electrode.

The positive and negative poles of the pair of binding posts designated by *I* are connected to the left-arm wire and right-arm wire, respectively, of the electrocardiographic recorder. The latter is set to record Lead I and is adjusted to have a sensitivity of 1 cm. of deflection per millivolt of input. This sensitivity will sometimes have to be reduced in order to accommodate a large deflection on the graph. The right-leg wire of the electrocardiograph is connected to the post designated as *To Ground of ECG or VCG*. The box surrounding the circuit may be grounded by means of the binding post marked *To Ground*.

For vectorcardiographic recording the amplifier for the horizontal deflection is connected to the binding posts marked *II*, and the amplifier for the vertical deflection is connected to the binding posts marked *III*. The output of the *I* pair of binding posts is then the third vectorcardiographic lead and is used for stereovectorcardiographic circuits or for independent scalar recording of the orthogonal leads.

S_1 represents the switch for selecting either the electrocardiographic leads or the vectorcardiographic leads. S_2, S_3, S_4, S_5, and S_6 represent switches which are used only for the electrocardiographic leads. S_2 is the switch which selects the various lead groups. *Routine* refers to the group of thirteen basic or screening leads. When S_2 is set on *Routine*, the S_3 switch is revolved through its thirteen positions from 1 through L to record all thirteen bipolar leads. The designation *Trans.* refers to the group of fourteen leads in the transverse plane. When S_2 is placed on *Trans.*, the S_4 switch may be revolved to record any or all of these

fourteen leads. The designations *Trans.'* and *Trans.*, on S_2 refer, respectively, to the superior and inferior set of transverse leads. When S_2 is placed at either of these positions, the S_4 switch is again utilized to select the desired leads. The designation *Longit.* on switch S_2 refers to the various leads recorded by the four longitudinal triangles. When S_2 is placed on *Longit.*, switch S_5 is first located at the desired thoracic point, E, C, A, I, or, in certain instances, an entirely new and independent exploratory point (*Explor.* on switch S_5), in which case the binding post in the upper left-hand corner of Fig. 8 is attached to any chosen point on the patient's thorax. After the adjustment of S_5, the switch designated S_6 is rotated to record any of the leads in the triangular plane selected by S_5. The symbolic designations of switch S_6 may be illustrated by consideration of the leads to be recorded when S_5 is set at E. In such a case, the symbol $\overset{\cdot\cdot}{\text{—}}$ would record E'', $\overset{\cdot}{\text{—}}$ would record E', — would record E, $\underset{\cdot}{\text{—}}$ would record $E_{\prime}$, $\underset{\cdot\cdot}{\text{—}}$ would record $E_{\prime\prime}$, and L would record Lead L. (The superscripts and subscripts for leads on the longitudinal planes have been defined previously in Table I.)

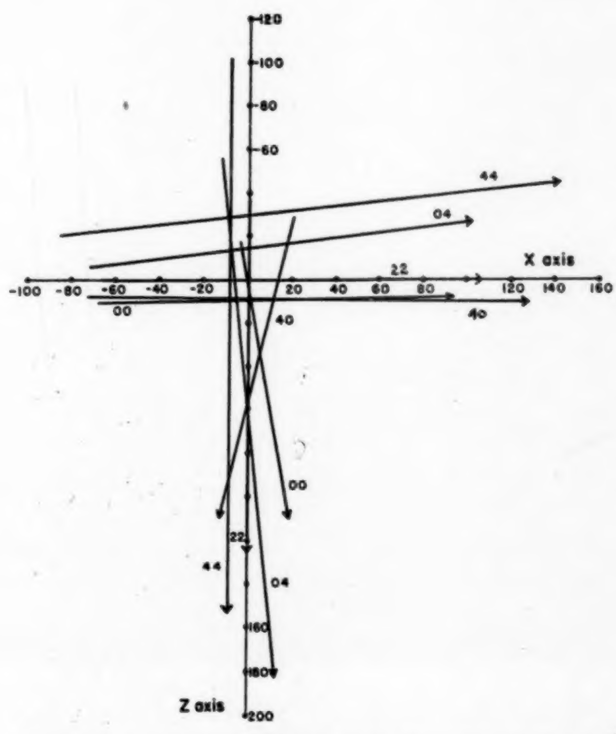

Fig. 7.—The lead vectors of leads X and Z for Frank's dipole locations 22, 04, 40, 44, and 00.

Switch S_7 is for vectorcardiographic recording and is utilized only when S_1 is set at *VCG*. Switch S_7 can then be rotated through F, S, and T to record the frontal, sagittal, and transverse vectorcardiographic planes on the screen of a cathode-ray oscilloscope when the vectorcardiographic amplifiers are attached to the *II* and *III* sets of posts as previously described. With the same rotation

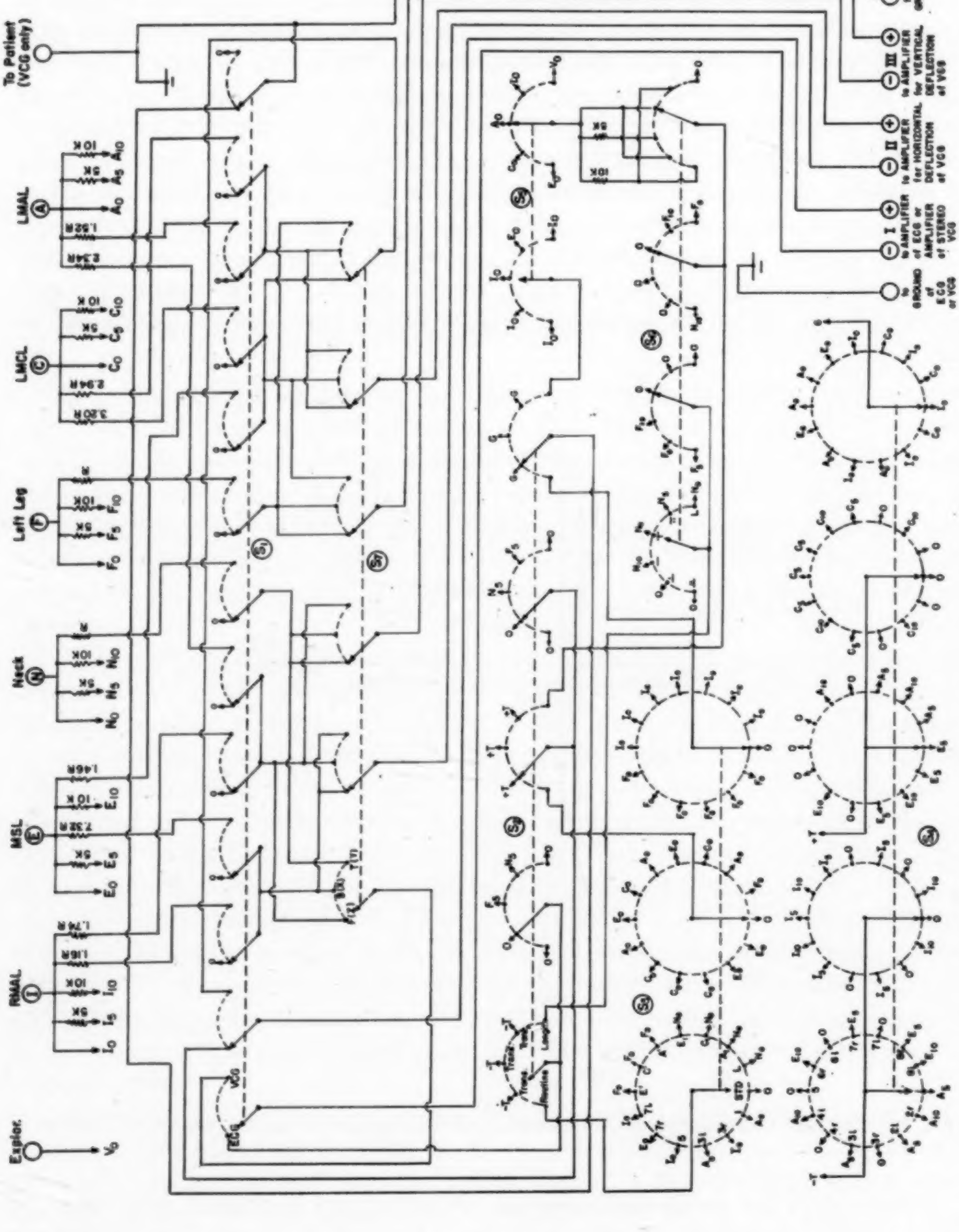

Fig. 8.—Wiring diagram of the switching circuit. See text. The resistances, R, may have any suitable value, such as 25,000 or 50,000 ohms.

of S_7, the scalar leads Z, X, and Y, indicated by the designation appearing in parentheses on the switch, are available for scalar recording or for stereovectorcardiography at the *I* set of binding posts.

As described in the legend of Fig. 9, certain of the dial positions for recording various electrocardiographic leads are printed in red rather than in white. The designations in red represent leads which are not obtained when the thirteen routine electrocardiographic leads are recorded. Thus, if the thirteen leads have just been recorded, only the leads printed in red need be recorded if it is undesirable to duplicate any of the routine leads. Moreover, when operating any given dial, all of the remaining dials should be placed on a white rather than on a red designation; only the switch in actual use then determines the circuit chosen.

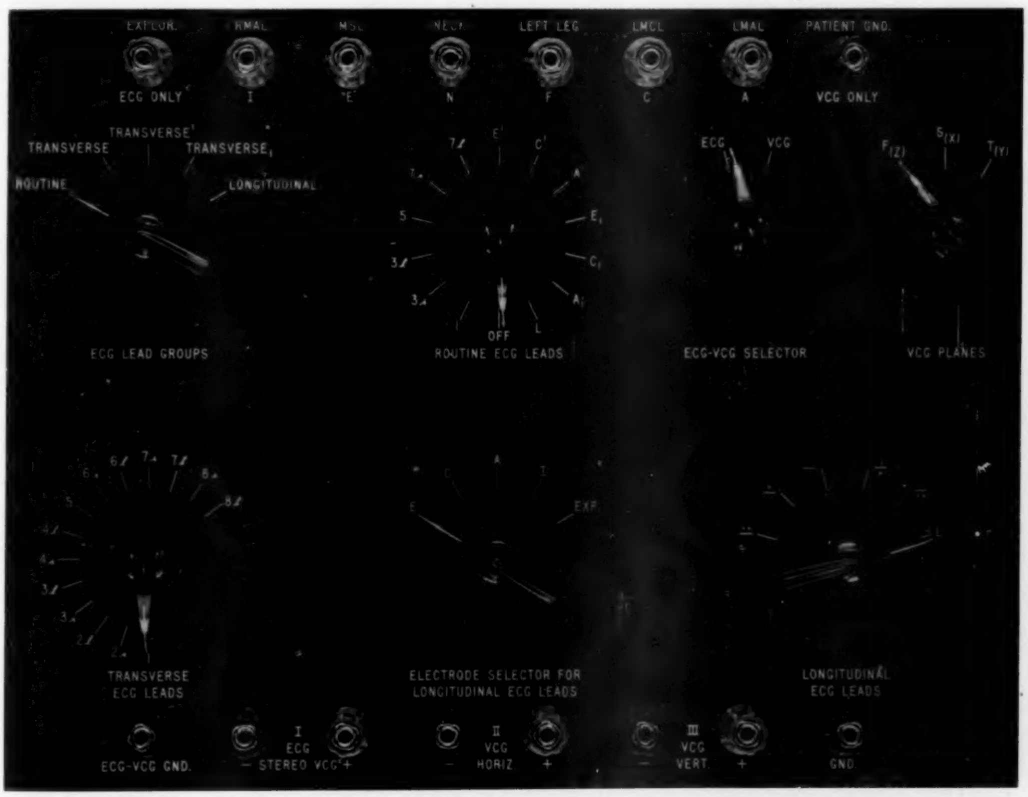

Fig. 9.—Face panel of the switching circuit. The four dials in the upper row represent, from left to right, switches S_2, S_3, S_1, and S_7. The three dials in the lower row represent, from left to right, switches S_4, S_5, and S_6. In this illustration, it cannot be appreciated that certain of the designations and symbols are printed in red, for the reasons given in the text. The red inscriptions are: Transverse′ and Transverse$_l$ on S_2; 2r, 2l, 4r, 4l, 6r, 6l, 8r, 8l on S_4; I and EXP. on S_5; and $\frac{+}{-}$, ——, and $\overline{+}$ on S_6.

Figs. 10 through 14 illustrate examples of the various groups of leads which can be recorded with the switching circuit. The thirteen routine leads are shown in Fig. 10. The right and left groups of transverse leads are illustrated in Figs. 11 and 12. Fig. 13 depicts the leads which may be recorded in the various longi-

tudinal planes. Fig. 14 shows the three scalar orthogonal leads which are available for vectorcardiographic use. The usual clinical electrocardiogram, consisting of standard, unipolar extremity, and precordial leads, is illustrated in Fig. 15. It is readily apparent that the individual from whom these tracings were recorded has an old antero-inferior myocardial infarction and right bundle branch block. Figs. 10 through 13 serve to illustrate both the wide variety of electrocardiographic leads which can be obtained with the switching circuit and also an effective method of grouping these leads to illustrate their interrelationships.

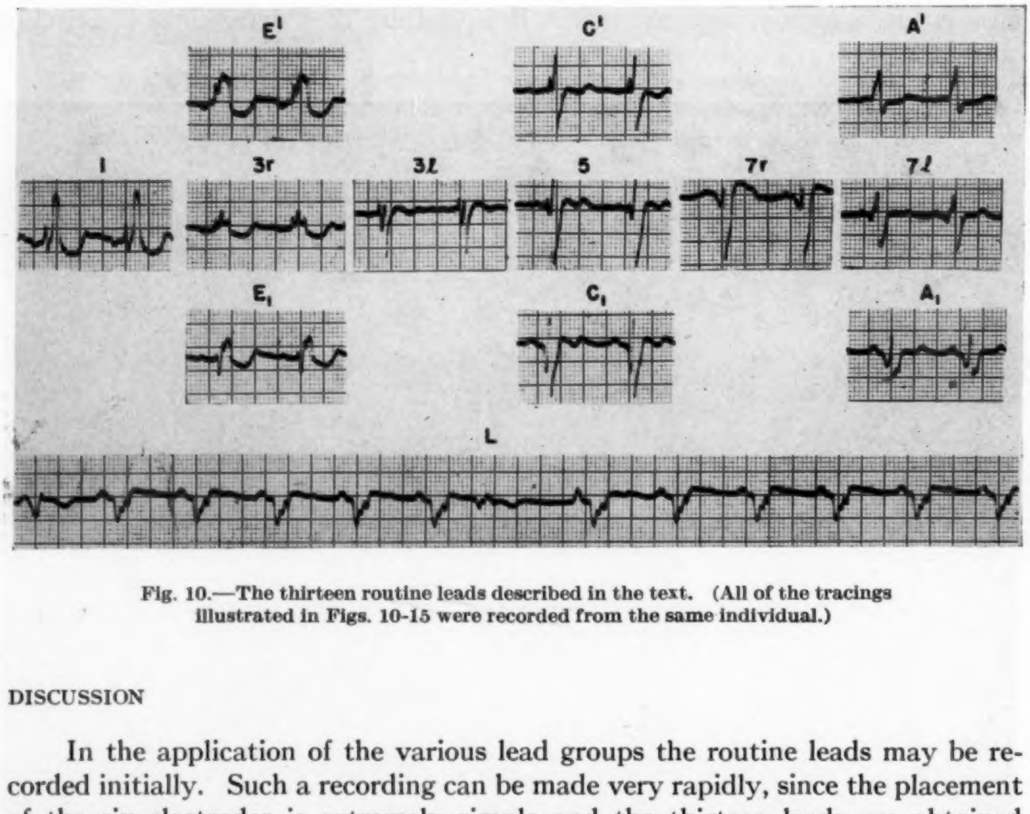

Fig. 10.—The thirteen routine leads described in the text. (All of the tracings illustrated in Figs. 10-15 were recorded from the same individual.)

DISCUSSION

In the application of the various lead groups the routine leads may be recorded initially. Such a recording can be made very rapidly, since the placement of the six electrodes is extremely simple and the thirteen leads are obtained merely by turning a dial. This is in contrast to the recording of the usual clinical electrocardiogram which requires six separate placements of the precordial electrode in addition to an electrode (including that used for grounding) on each of the four extremities. If the thirteen routine leads, recorded from a variety of vantage points, are completely normal, or if they do not differ significantly from a previous tracing, no more leads need be taken. If there is any suggestion of an abnormality which might be clarified by the study of additional leads, these can be obtained quickly without any change in the positions of the electrodes.

Mathematical methods for analyzing the structure of leads have been described recently, and the reader is referred to this publication[7] for a complete discussion of the techniques involved. Table II lists the results of such analyses

Fig. 11.

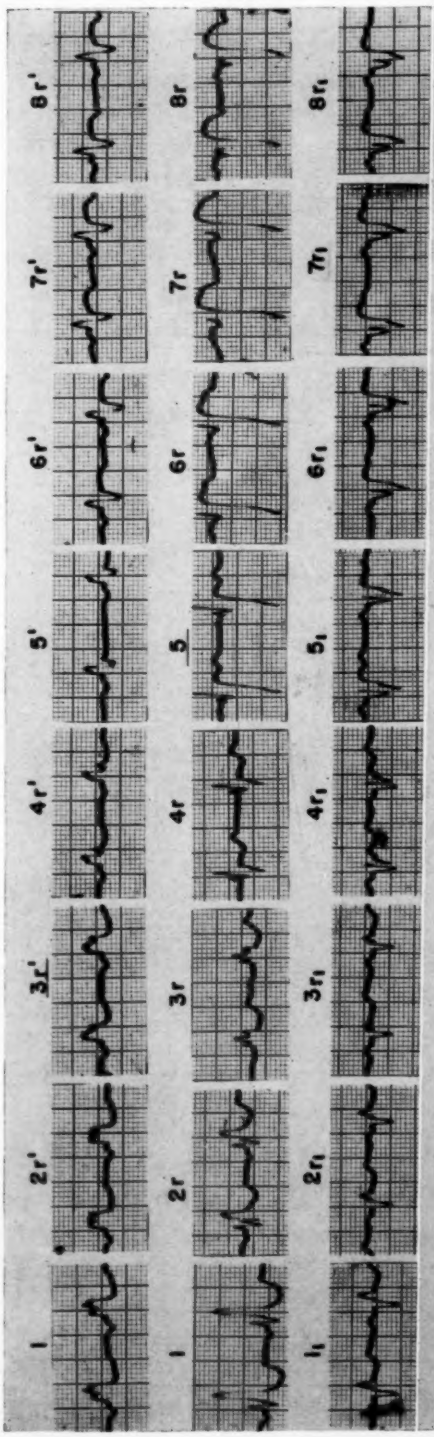

Fig. 12.

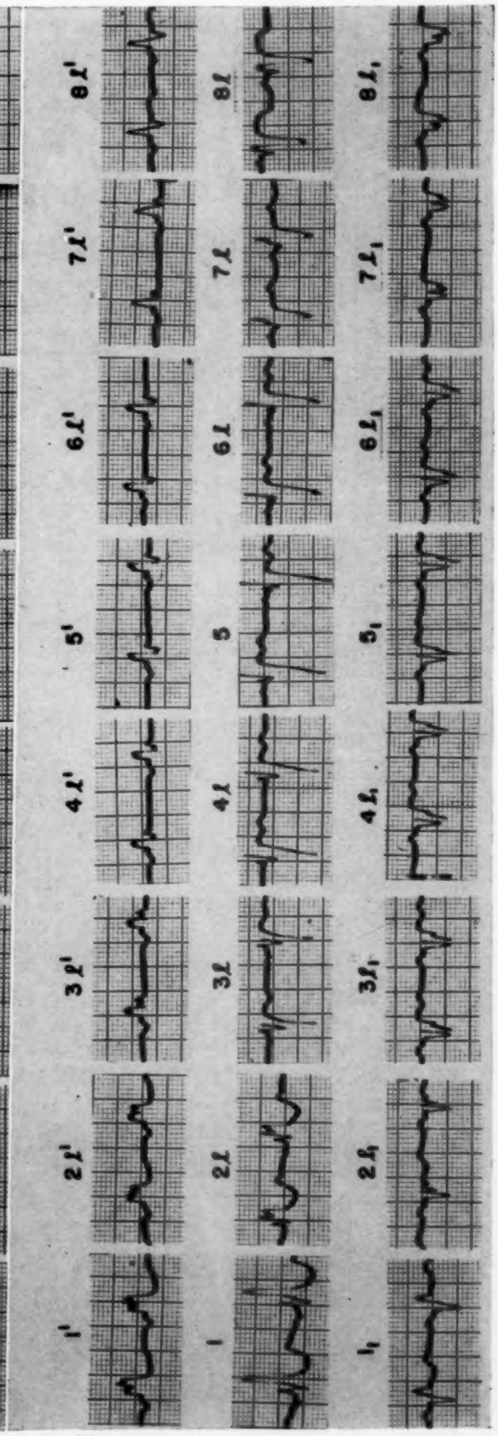

Fig. 11.—The three sets of right (r) transverse leads described in the text.
Fig. 12.—The three sets of left (l) transverse leads described in the text.

TABLE II

	LEAD	FRANK UNITS FOR DIPOLE NO. 22			FRANK UNITS FOR ALL 71 DIPOLES				MATHEMATICAL ANALYSIS				
		x	z	j	X	Z	J	J'	E_t^2	E_m^2	E_d^2	E'^2_m	E'^2_d
ECG LEADS	1	−154.5	187.5	243.0	−245.8	278.0	371.1	375.4	13.21	11.56	1.57	11.29	1.56
	3r	10.7	150.0	150.4	−62.7	206.6	215.9	225.2	50.90	44.82	6.51	41.09	5.63
	3l	36.6	170.5	174.4	113.4	295.4	316.4	361.7	54.38	34.03	17.53	24.92	16.44
	5	201.8	133.0	241.7	296.5	224.0	371.6	385.3	24.74	19.52	4.59	18.07	4.51
	7r	191.1	−17.0	191.9	359.2	17.3	359.6	421.7	64.99	40.49	19.71	27.91	18.21
	7l	165.2	−37.5	169.4	183.1	−71.4	196.6	199.1	12.53	10.70	1.76	10.42	1.69
VCG LEADS	X	176.2	− 0.1	176.2	230.3	0.7	230.3	233.8	6.26	4.09	1.79	3.95	1.76
	Z	0.0	160.7	160.7	−28.4	242.6	244.2	250.8	14.80	10.99	3.30	10.37	3.25
MATHEMATICAL FORMULAE		- - - - - - - -	- - - - - - - -	$j = \sqrt{x^2 + z^2}$	$X = \frac{\Sigma x}{71}$	$Z = \frac{\Sigma z}{71}$	$J = \sqrt{X^2 + Z^2}$	$J' = \frac{\Sigma j}{71}$	$E_t^2 = \frac{\Sigma j^2}{J^2} - 71$	$E_m^2 = \frac{\Sigma j^2}{J^2} - \frac{2\Sigma j}{J} + 71$	$E_d^2 = 142 - \left(\frac{2}{71\,J}\right)\left(\Sigma x \sum \frac{x}{j} + \Sigma z \sum \frac{z}{j}\right)$	$E'^2_m = \frac{\Sigma j^2}{J'^2} - 71$	$E'^2_d = 71 - \left[\frac{1}{71}\right]\left[\left(\sum \frac{x}{j}\right)^2 + \left(\sum \frac{z}{j}\right)^2\right]$

of the six routine bipolar transverse leads and orthogonal leads X and Z. The various formulae used are given at the bottom of the columns. The data upon which these calculations were made were those published by Frank[5] for 71 dipole locations. Since 140 degrees of freedom are involved in both the numerator and denominator, a probability of less than 0.2 per cent is achieved when a variance ratio of two E^2 values exceeds 1.69.

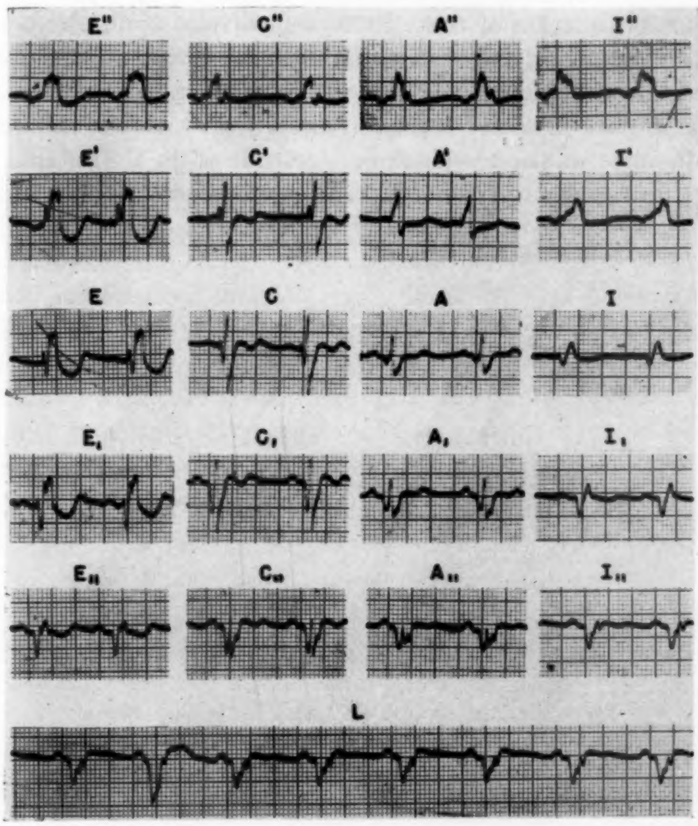

Fig. 13.

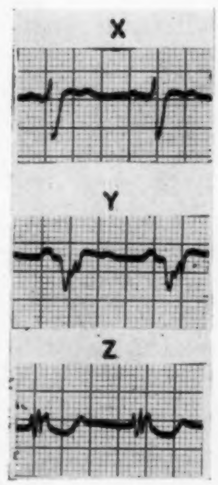

Fig. 14.

Fig. 13.—The twenty-one longitudinal leads described in the text.
Fig. 14.—The three orthogonal vectorcardiographic leads described in the text.

The values of E'^2_m are relatively high in the case of leads 3r, 3l, 5, and 7r. The multiple vectors of these leads, therefore, vary considerably in magnitude, suggesting that they record preferentially from certain areas of the heart.[7] These leads are analogous to the precordial leads of the usual clinical electrocardiogram, as are leads 1 and 7l which correspond most closely in magnitude and direction to leads V_1 and V_6, respectively. It should be noted (Table II) that leads 1 and 7l show only moderately high values of E'^2_m and very low values of E'^2_d, indicating that these leads record practically unidirectional components of the electromotive forces arising in many regions of the heart. Moreover, the mean directions of these leads, particularly that of lead 1, are favorably located for the diagnosis of left and right ventricular hypertrophy.

Data are not available for analyzing the remaining bipolar leads, E′, $E_{\prime}$, C′, $C_{\prime}$, A′, $A_{\prime}$. Lead-field considerations, however, suggest that if values of $E_m^{\prime 2}$ could be calculated for these leads, they would be relatively high. On the other hand, leads representing the difference in potential between a point and a network of points or between two networks of points, such as the majority of leads listed in Table I, would have lower values of $E_m^{\prime 2}$ and would be less discriminative than the bipolar leads representing the difference in potential between two points. The chief function of these leads is to demonstrate the temporal relationship between the peaks and nadirs of the bipolar leads. It should be pointed out that the discriminative capacity of exploratory electrocardiographic V leads taken at higher or lower levels on the chest than the usual V leads decreases as the distance of the exploratory electrode from the heart increases.

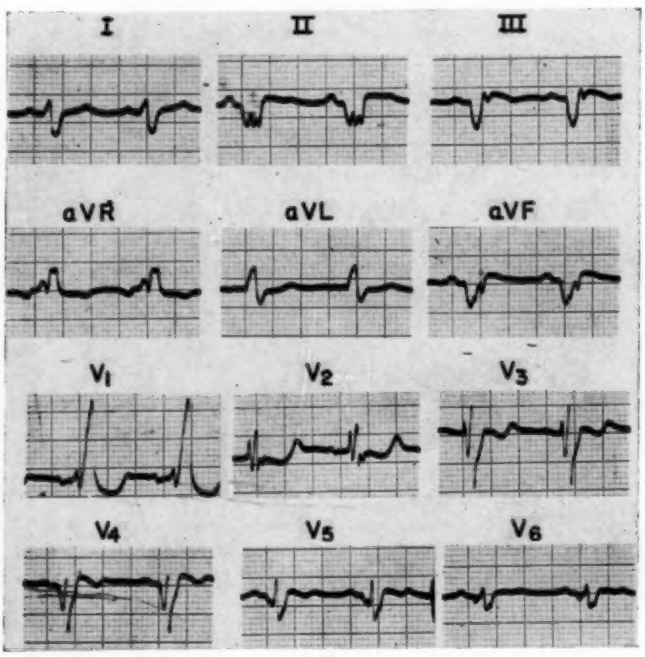

Fig. 15.—The usual twelve-lead clinical electrocardiogram.

The value of E_t^2 is relatively low in the case of lead X, suggesting that this lead should be satisfactory for vectorcardiography. In view of its higher value of E_t^2, lead Z is significantly inferior to lead X. However, it is difficult to develop a sagittal lead with uniform multiple lead vectors without resorting to more complicated electrodes[2] or numerous electrode placements.[8,9] It should be noted that the value of E_t^2 of lead Z is much lower than the corresponding values of leads 3r and 3l which form the network components of lead Z, indicating a considerable increase in the uniformity of the lead field when these two leads are combined. Data are not available for calculating E_t^2 for lead Y, but there is good lead-field evidence that this value would be relatively low.

In the study of the electrical field of the heart, two basically divergent approaches are available: (1) The simultaneous recording of three leads which are orthogonal and possess uniform lead fields. If the assumption is then made that the heart behaves with respect to body surface leads like a single dipole of fixed location but variable moment, there is no advantage in recording any other body surface leads. (2) Consecutive recording of many leads from multiple points on the body surface (pairing each against the Wilson central terminal or some other common electrode or network). If the assumption is made that the heart behaves in a significantly nondipolar manner with respect to a wide variety of surface leads, this approach may be expected to yield information not obtainable with the first approach.

There is evidence favoring each of the divergent theoretical considerations underlying these two approaches, and it is likely that both could be profitably applied in a complementary manner. However, some vectorcardiographic lead systems are too elaborate to be practical clinically, and the recording of multiple body surface leads utilizing many electrode sites is also extremely time-consuming. The primary purpose of the electrode placement described in this communication is to provide a very simple means of obtaining clinically satisfactory, if not theoretically ideal, vectorcardiographic leads, and, with the same electrode placement, to permit the selection of a wide variety of electrocardiographic leads from many vantage points.

SUMMARY

A method of placing six electrodes is described for recording a wide variety of electrocardiographic leads and, with the use of a seventh electrode as a ground, for obtaining three approximately orthogonal leads for vectorcardiographic purposes. The detailed circuitry of a switching box for such recording is given.

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Studies on the Nature of the S-T Segment Changes

I. S-T Changes Influenced by Varying Concentrations of Oxygen in Experimental Coronary Artery Occlusion in the Dog

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Coronary artery disease is the cause of almost one million cases of myocardial infarction and nearly a quarter of a million deaths annually in the United States. For many years the treatment has been essentially rest and sedation, and in more recent years, the use of oxygen inhalation and anticoagulants.

Of the quarter of a million deaths, less than 10 per cent were due to irreversible myocardial destruction. In the vast majority of persons, death possibly resulted, in those with capable beating hearts, from ventricular fibrillation due to an uneven distribution of myocardial oxygen. This condition also produces electrocardiographic S-T segment deviation. Extensive experiments on dogs by Beck and co-workers[1,2] imply that the addition of only a few cubic centimeters per minute of arterial blood to a cyanotic myocardial region could reduce the unevenness of oxygen distribution, and therefore possibly prevent ventricular fibrillation and death in man.

In the surgery of coronary artery disease in man the operative method of Beck duplicates the above-mentioned procedure by creating intercoronary channels. The results were good to excellent in 4 out of 5 patients thus operated, and the operative mortality was 0 in a series of 100 consecutive patients.[3] The extent to which this operation may reduce the death rate in coronary artery disease remains to be established. Editorials of the British journal *Lancet* state that "there is a good case for giving the operation (Beck) an extensive trial, and the results so far offer grounds for sober optimism."[4]

The purpose of the present paper was to study the relationship between a myocardial oxygen gradient and the S-T segment changes, both in magnitude and morphology, during experimental acute coronary artery occlusion in dogs, and to observe the incidence of ventricular fibrillation during these experimental procedures. Additional methods for subsequent studies are also suggested.

The experiments of this report were performed at the Galveston Medical School, Galveston, Tex.
Supported in part by a grant from the Medical Research Foundation of Texas.
Received for publication March 2, 1959.
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EXPERIMENTS AND OBSERVATIONS

Thirteen mongrel dogs, each weighing between 8 and 12 kilograms, were employed in the present study. The narcotic, Seconal*, was injected intraperitoneally in a dosage of 30 milligrams per kilogram of body weight. The dog lay on the right side of its back, and the sternum was split and retracted. The pericardium was opened and sutured to the chest wall as a cradle for the heart. A respirator and an anesthesia machine were used alternately.

Under respiration of room air the exposed heart appeared uniformly pink (Fig. 1,*a*). Acute myocardial infarction at the apex region was produced by ligating two or three branches of the left descending coronary artery. Immediately thereafter this region became uniformly cyanotic (Fig. 1,*b*). An anesthesia machine was connected in order to permit the administration of a mixture of oxygen and nitrogen at any desired concentration. When a gas mixture of decreasing oxygen and increasing nitrogen was administered, the previously pink region gradually became cyanotic. At 0 per cent oxygen and 100 per cent nitrogen the entire heart became uniformly cyanotic (Fig. 1,*c*). When the gas mixture was given at decreasing nitrogen and increasing oxygen concentrations, the heart gradually returned to its original pink color, except that the apex region remained cyanotic and unchanged (Fig. 1,*d*). When the oxygen reached 50 to 100 per cent concentration, the pink color became more and more intense.

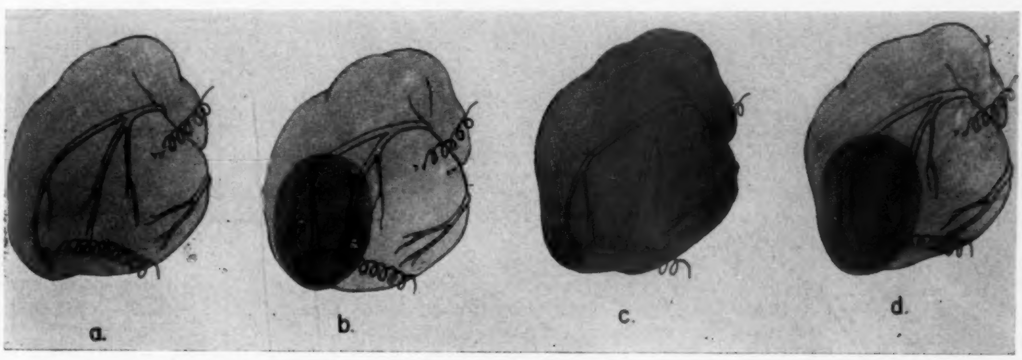

Fig. 1.—The exposed dog heart with left descending coronary artery and its branches. *a*, The site of the two needle electrodes at the base and at the apex. Before ligation of the coronary artery the myocardium was uniformly pink. *b*, Two ligatures were applied as shown. The apex region became cyanotic, sharply bounded by pink myocardium. *c*, A uniformly cyanotic heart. *d*, Similar in appearance to *b*, except that the pink region was apparently more bright than in *b*.

When the heart was either uniformly pink or uniformly cyanotic, the distribution of oxygen within the myocardium was assumed to be even. When the heart was partially pink and partially cyanotic, the distribution of oxygen within the myocardium became uneven. This suggested an oxygen gradient across the two myocardial regions. This was manifested as S-T segment deviation in a bipolar lead connecting the two regions. If the positive electrode was situated at the cyanotic region and the negative electrode at the pink region, an elevation of the S-T segment resulted.

In the present study a bipolar subepicardial lead was employed as described elsewhere.[5] The positive electrode was placed at the apex, and the negative electrode at the base. These electrodes consisted of two curved surgical needles superficially penetrating the myocardium. The adequacy of this method was proved. Thus, before ligation of the coronary artery the bipolar lead usually recorded an isoelectric S-T segment despite superficial myocardial penetration. Occasionally, there was an S-T segment deviation of insignificant magnitude which could be brought to the base line with ease, as illustrated later. The recording instrument was the Sanborn Viso-Cardiette.

***Secobarbital sodium, donated by Eli Lilly and Company, Indianapolis, Ind.**

INTERPRETATION OF THE ELECTROCARDIOGRAMS

1. *The Bipolar Subepicardial Lead.*—Before ligation of the coronary artery the S-T segment in the bipolar subepicardial lead usually appeared as isoelectric (Figs. 2,*c*, 7,*c*, 8,*c*, and 9,*d*). Because the injury potential caused by superficial myocardial penetration at each electrode was presumably the same, no difference in potential could be recorded in the bipolar lead. On the other hand, in a unipolar lead connected from either electrode with the Wilson central terminal the S-T segment elevation was of considerable height and had seemingly equal magnitude. (The unipolar base lead is shown in Figs. 2,*a*, 7,*a*, and 8,*a*, and the unipolar apex lead is shown in Figs. 2,*b*, 7,*b*, and 8,*b*).

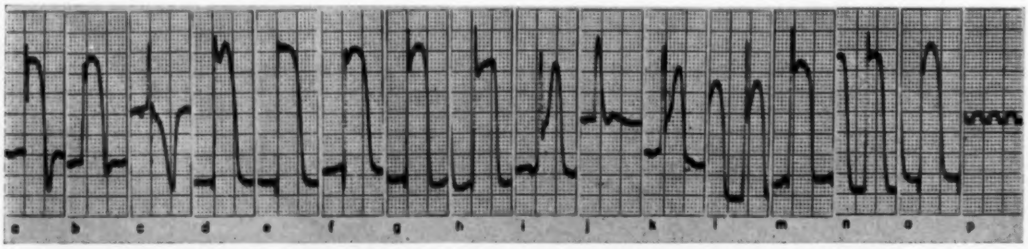

Fig. 2.—*a*, Unipolar subepicardial base lead. High S-T segment elevation. *b*, Unipolar subepicardial apex lead. High S-T segment elevation. *c*, Bipolar subepicardial lead. Isoelectric S-T segment. *d*, Immediately after ligation of the coronary artery. High S-T segment elevation. *e*, *f*, *g*, *h*, *i*, Gradual lowering of the S-T segment elevation by gradual reduction of oxygen from 50 per cent down and increase of nitrogen from 50 per cent up. *j*, At 0 per cent oxygen and 100 per cent nitrogen the S-T segment became isoelectric. *k*, *l*, *m*, *n*, *o*, Gradual increase of the S-T segment elevation by gradual increase of oxygen from 0 to 100 per cent and reduction of nitrogen from 100 to 0 per cent. The S-T segment elevation in *o* was presumably maximum. *p*, Calibration: 0.2 cm. = 1 millivolt. (Same calibration for all subsequent electrocardiograms.)

Occasionally, a deviation of the S-T segment was observed in the bipolar lead upon insertion of the needle electrodes (Fig. 9,*a*). A gentle tap on the electrode opposite to the deviation would usually bring the S-T segment to the base line (Fig. 9,*d*). If the tap was not gentle, deviation of the S-T segment toward the referred electrode usually resulted (Fig. 9,*b* and *c*).

In passing, it may be stated that an S-T segment elevation was recorded when a cotton-tipped unipolar electrode was placed in the cyanotic region, and an S-T depression, when it was placed in the pink region.[5] Cotton-tipped electrodes were not adequate for the present study because the beating heart moved under such electrodes. A unipolar subepicardial lead was also not adequate for the present purpose despite good fixation with a needle electrode. Thus, in a unipolar subepicardial base lead it was not possible to estimate the component of the S-T segment depression caused by ligation of the coronary artery that was hidden in the S-T segment elevation caused by insertion of the needle electrode (Figs. 5,*b* and 7,*d*); and in a unipolar subepicardial apex lead it was not possible to distinguish the S-T segment elevation caused by ligation of the coronary artery from that caused by insertion of the needle electrode (Figs. 5,*c* and 7,*e*). Therefore, the bipolar subepicardial lead was found to be necessary for the present study.

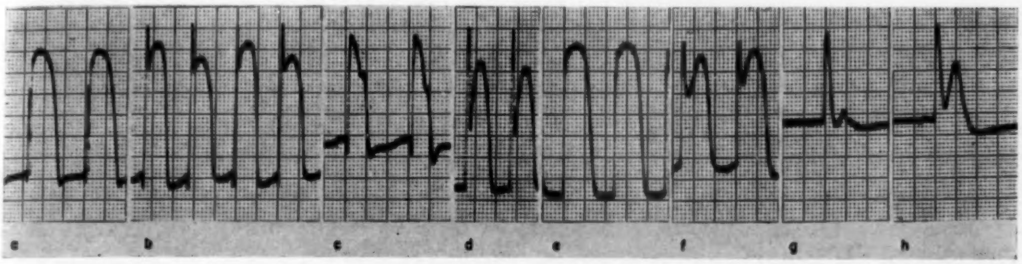

Fig. 3.—*a*, Bipolar subepicardial lead after ligation of the coronary artery and 100 per cent oxygen. Very high S-T segment elevation. *b*, Electrical alternans of the S-T segment during anoxia. The S-T segment elevation was of the same height alternately. *c*, Widened QRS complex during continued anoxia. *d*, QRS complex became narrow when oxygen was administered. *e*, Very high S-T segment elevation as the procedure continued. *f*, Lowering of the S-T segment elevation as oxygen was reduced. *g*, Isoelectric S-T segment at 0 per cent oxygen and 100 per cent nitrogen. *h*, Agonal S-T segment elevation accompanied by a steeple type of T wave as 100 per cent nitrogen was continued.

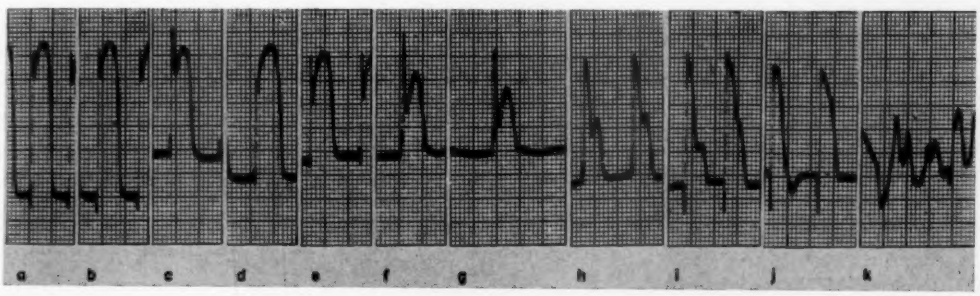

Fig. 4.—*a*, Bipolar subepicardial lead after ligation of the coronary artery and during respiration of room air. High S-T segment elevation. *b*, Upon administration of 20 per cent oxygen the S-T segment elevation remained unchanged. *c*, S-T segment elevation decreased in height as oxygen was reduced to 10 per cent. *d*, S-T segment increased to maximum as 100 per cent oxygen was administered. *e*, *f*, *g*, Gradual decrease of S-T segment elevation as oxygen was gradually decreased to 10 per cent. *h*, Widened QRS complex as oxygen reached 5 per cent. *i*, Merging of the elevated S-T segment into the wide QRS complex. *j*, Disappearance of the S-T segment into the QRS complex. *k*, Ventricular fibrillation and sudden death immediately after administration of 100 per cent oxygen.

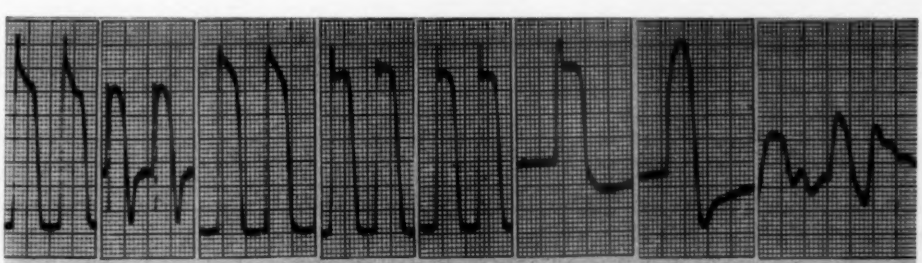

Fig. 5.—*a*, Bipolar subepicardial lead immediately after ligation of the coronary artery. High S-T segment elevation. *b*, Subsequent unipolar base lead. High S-T segment elevation. *c*, Subsequent unipolar apex lead. High S-T segment elevation. *d*, Bipolar subepicardial lead one hour after ligation. Height of the S-T segment elevation was apparently unchanged. However, it became a plateau, whereas in *a* it was a slope. *e*, Slight decrease of S-T segment elevation during anoxia. *f*, Widened QRS complex as this procedure continued. *g*, Final disappearance of the S-T segment in the wide QRS complex. *h*, Ventricular fibrillation and death occurred immediately after administration of 100 per cent oxygen.

2. *The General Course of the S-T Segment Elevation.*—Before occlusion, the S-T segment was isoelectric (Fig. 2,*c*), with both needle electrodes placed in the pink myocardium (Fig. 1,*a*). After occlusion, the myocardium surrounding the apex electrode became cyanotic, whereas the myocardium surrounding the base electrode remained pink (Fig. 1,*b*). The corresponding electrocardiogram during the respiration of room air showed an S-T segment elevation of considerable height (Fig. 2,*d*). When the dog was given a gas mixture of 50 per cent oxygen and 50 per cent nitrogen, the pink region became even more intense and the S-T segment elevation was correspondingly higher (Fig. 2,*e*). Then, when the oxygen was gradually reduced from 50 to 0 per cent, and the nitrogen increased from 50 to 100 per cent, the pink region of the myocardium gradually became cyanotic, until finally the entire heart was uniformly cyanotic (Fig. 1,*c*). Corresponding electrocardiograms revealed a gradual decrease in the elevation of the S-T segment (Fig. 2,*f*, *g*, *h*, *i*), which became isoelectric at 0 per cent oxygen (Fig. 2,*j*).

When the oxygen was increased gradually from 0 to 100 per cent and the nitrogen decreased from 100 to 0 per cent, the S-T segment showed a gradual elevation (Fig. 2,*k*, *l*, *m*, *n*), and the pink region gradually reappeared on the myocardium. At 100 per cent oxygen, the S-T segment reached its highest level of elevation (Fig. 2,*o*), and the pink myocardium assumed even more brightness than it had had immediately after ligation of the coronary artery.

3. *S-T Segment Electrical Alternans.*—This electrical phenomenon is illustrated in Fig. 3,*b*. It shows that elevation of the S-T segment was of the same magnitude alternately. This electrical phenomenon occurred occasionally during the anoxia test.

4. *Agonal S-T Segment Elevation.*—From the dying heart at 0 per cent oxygen administration an agonal S-T segment elevation associated with a steeple type of T wave was recorded after the S-T segment had been returned to the base line. Such a pattern is illustrated in Fig. 3,*h*.

5. *Merging of the S-T Segment.*—During the procedure of reducing the administration of oxygen one could occasionally observe the following sequential changes in the electrocardiogram: gradual widening of the QRS complex, merging of the S-T segment into the QRS complex, and, finally, disappearance of the S-T segment into a broad QRS complex. These changes are illustrated in Figs. 4,*h*, *i*, *j*, and 5*f*, *g*.

6. *Temporal and Multiligature Effect.*—Generally, the height of elevation of the S-T segment remained unchanged for a period of one hour after acute coronary artery occlusion, but morphologic changes of the S-T segment could appear in this period. In Fig. 5, *d* was recorded one hour after *a*, the latter having been taken immediately after occlusion of the coronary artery. Note that the height of the S-T segment take-off remained apparently unchanged, while morphologically the S-T segment changed from a slope to a plateau. The elevation of the S-T segment was generally in a direct ratio to the number of arterial branches ligated. In Fig. 6, *a* was recorded immediately after two arterial branches had been ligated, and *b* was recorded after an additional branch had been ligated. Note that the S-T segment take-off in *b* is higher than in *a*.

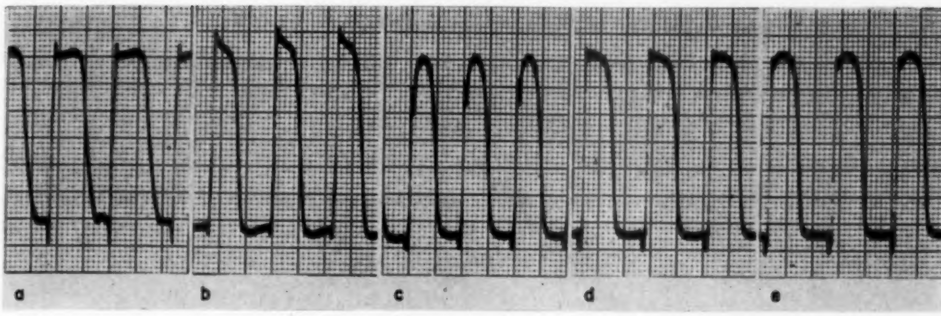

Fig. 6.—*a*, Bipolar subepicardial lead after ligation of two coronary artery branches. High take-off of S-T segment elevation. *b*, After ligation of an additional branch the take-off of the S-T segment elevation was higher. *c*, Very high S-T segment elevation upon administration of 100 per cent oxygen. *d*, S-T slightly lowered after one hour of respiration of room air. *e*, S-T segment went up again upon administration of 100 per cent oxygen.

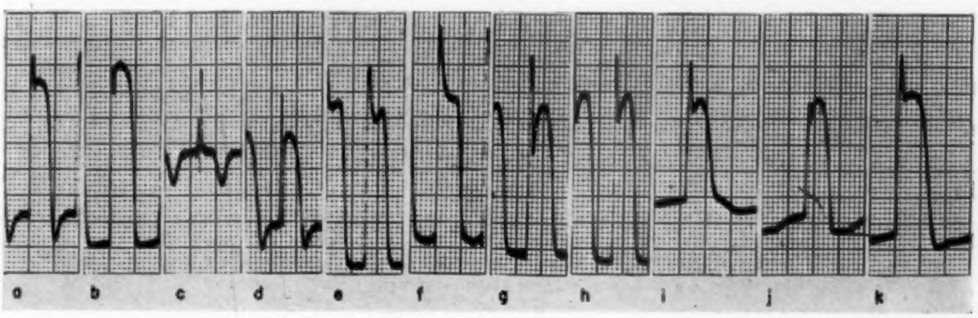

Fig. 7.—*a*, Unipolar subepicardial base lead before ligation of the coronary artery. High S-T segment elevation. *b*, Unipolar subepicardial apex lead before the ligation. High S-T segment elevation. *c*, Bipolar subepicardial lead before the ligation. Isoelectric S-T segment. *d*, Unipolar subepicardial base lead one hour after the ligation. Moderate S-T segment elevation. *e*, Unipolar subepicardial apex lead one hour after the ligation. Moderate S-T segment elevation. *f*, Bipolar subepicardial lead one hour after the ligation. Moderate S-T segment elevation. *g*, *h*, *i*, *j*, Gradual increase of S-T segment elevation during administration of oxygen. *k*, Decrease of the S-T segment elevation upon respiration of room air.

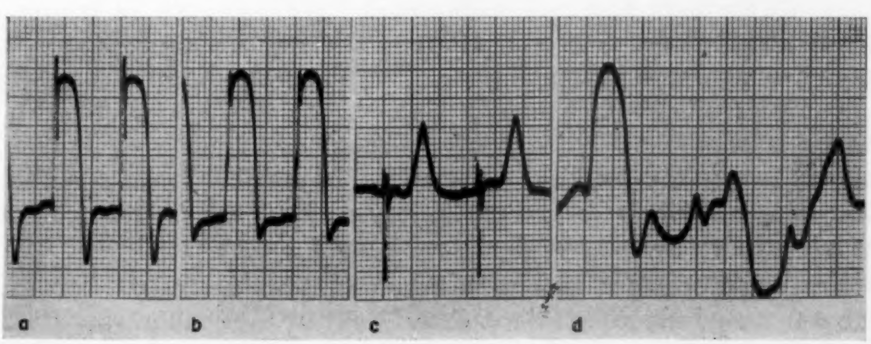

Fig. 8.—*a*, Unipolar subepicardial base lead. High S-T segment elevation. *b*, Unipolar subepicardial apex lead. High S-T segment elevation. *c*, Bipolar subepicardial lead. Isoelectric S-T segment. *d*, Ventricular fibrillation and sudden death occurred immediately after ligation of the coronary artery.

7. *Ventricular Asystole and Fibrillation.*—When oxygen was continued at 0 per cent and nitrogen at 100 per cent, the uniformly cyanotic heart dilated, became asystolic, and died. Immediately following the re-establishment of an oxygen gradient by administration of pure oxygen after the myocardium had become uniformly cyanotic, two instances of ventricular fibrillation and sudden death occurred (Figs. 4,*k* and 5,*h*). In one of the 13 dogs ventricular fibrillation and sudden death occurred immediately after the ligation of two coronary arterial branches (Fig. 8).

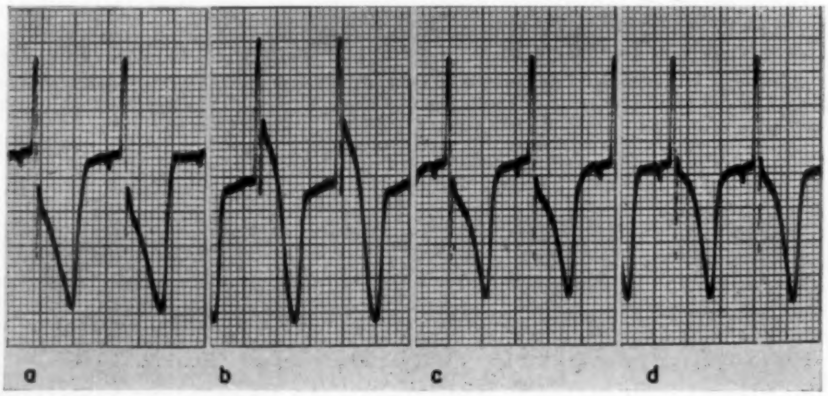

Fig. 9.—*a*, Bipolar subepicardial lead before ligation of the coronary artery. Depression of the S-T segment. *b*, Elevation of the S-T segment resulted from a tap on the apex electrode. *c*, Slight depression of the S-T segment resulted from a gentle tap on the base electrode. *d*, Finally, an isoelectric S-T segment was achieved by a gentle tap on the apex electrode.

DISCUSSION

The S-T segment was usually isoelectric both before and after ligation of the coronary artery at 0 per cent oxygen administration. There was an elevation of the S-T segment after ligation and with inhalation of oxygen. The elevation of the S-T segment after ligation was directly related to the amount of oxygen administered. At 100 per cent oxygen it reached its maximum height.

Before ligation the heart was uniformly pink. The distribution of oxygen within the myocardium was presumably even. After ligation of two or three branches of the left descending coronary artery the apex became cyanotic, whereas the rest of the myocardium remained pink. When the distribution of oxygen within the myocardium became uneven, an oxygen gradient across the two myocardial regions appeared. When a large amount of oxygen was administered, the pink region became brighter and the oxygen gradient became higher. At 0 per cent oxygen the heart became uniformly cyanotic and the oxygen gradient disappeared.

In these experiments a bipolar subepicardial lead was used. The positive electrode penetrated the myocardium superficially at the cyanotic apex, whereas the negative electrode was located at the pink base. The oxygen gradient produced an elevation of the S-T segment, and the higher the oxygen gradient, the higher the S-T segment elevation became.

In acute occlusion of the coronary artery the S-T segment deviation could not be explained entirely by the theory of injury current, because in a uniformly cyanotic heart with acute occlusion of the coronary artery the S-T segment was isoelectric despite the injury. Instead, as shown in the present study, the myocardial oxygen gradient appeared to be one of the explanations.

The oxygen gradient that caused S-T segment elevation could be defined as the difference between the myocardial oxygen availability at the pink region and that at the cyanotic region surrounding both electrodes. However, the anesthesia machine was not an adequate measuring apparatus for this purpose, nor were we certain about the residual circulation in the cyanotic region after the ligation. Therefore, it was thought that an associated study of polarographic oxygen at these two regions might possibly provide a more accurate relationship between oxygen gradient and S-T segment elevation. We presently became aware of the study by Sayen and associates,[8] who observed that polarographic oxygen recordings with electrodes inserted into the myocardium were a more sensitive parameter than the nearby epicardial unipolar electrocardiographic tracings in response to the experimental acute coronary artery occlusion or critical narrowing. Among various factors that selectively influence the two phenomena the effect of obstruction or reduction of coronary flow on local oxygen availability might be more profound at subepicardial layers than at the epicardial surface. We thought the difference in sensitivity of both phenomena might well be studied from the same electrode positions, namely, from the bipolar subepicardial lead.

Three types of morphologic changes of the S-T segment were observed. They were classified as S-T segment electrical alternans, agonal S-T segment elevation, and merging of the S-T segment. These changes also occurred in a few instances during the anoxia test. They probably indicated severity of myocardial damage, although their genesis remained obscure. It is suggested that these changes be studied at the cellular level by means of ultra-microelectrodes inserted into the two regions, in the hope of locating the site of the disturbances.

Beck and associates postulated that in human coronary artery disease the uneven distribution of myocardial oxygen between pink region and cyanotic region was the cause of a current of oxygen differential manifested by S-T segment deviation.[1,3,6] At critically high levels the heart would become electrically unstable and fibrillate. They assumed that this was the cause of death in the vast majority of the cases. In dog experiments they demonstrated that death was prevented by adding only a few cubic centimeters per minute of arterial blood distal to the occlusion. In human coronary artery disease the operative methods of Beck duplicate this lifesaving procedure. Indeed, the results were good to excellent in 4 out of 5 patients. Their operative mortality in a series of 178 patients was only 1.2 per cent, and in another series of 100 patients it was 0 per cent. In comparison with medically treated cases it began to appear that the operation might possibly reduce the mortality from the disease.[6] Therefore, surgery should be seriously considered in human coronary artery disease, and medical care should only be indicated when the severity does not permit operation.

Brofman and associates assumed a fibrillation index for the production of ventricular fibrillation.[6] According to these authors the index was directly related to the current of oxygen differential (or oxygen gradient) and inversely related to the fibrillation threshold. In the present study on 13 mongrel dogs, three instances of ventricular fibrillation occurred. One instance occurred immediately after ligation of the coronary artery, while the other two occurred immediately after the administration of pure oxygen in a uniformly cyanotic heart. Sayen and associates[8] observed three instances of ventricular fibrillation in their series. In one dog the clamp had just been released after occlusion, and the other two dogs were breathing pure oxygen after occlusion. Thus, one might postulate that the suddenness of creating an oxygen gradient across the myocardium was the cause of ventricular fibrillation in both studies. In addition, in Sayen's series the existing high oxygen gradient was probably the cause of death in the remaining two dogs. This implied that the beneficial effect of oxygen therapy in human coronary artery occlusion was doubtful.

SUMMARY AND CONCLUSIONS

1. The myocardial oxygen gradient was apparently the major cause of S-T segment elevation in acute occlusion of the coronary artery in dogs.
2. The S-T segment was not necessarily related to the total myocardial oxygen concentration. Thus, an isoelectric S-T segment was recorded both from uniformly pink hearts and uniformly cyanotic hearts.
3. The suddenness of creating a myocardial oxygen gradient could be one cause of ventricular fibrillation and sudden death.
4. An associated study of polarographic oxygen at pink region and cyanotic region of the myocardium could possible provide a more quantitative correlation between oxygen gradient and S-T segment elevation.
5. Three types of morphologic changes of the S-T segment were observed. These were the S-T segment electrical alternans, the agonal S-T segment elevation, and the merging of the S-T segment. These changes occurred occasionally during the anoxia test. Their genesis is obscure. A study of these changes should be made at the cellular level by means of ultra-microelectrodes, in hopes of locating the site of the disturbance.
6. Surgery should be seriously considered in human coronary artery disease. The present study implies that the beneficial effect of oxygen therapy in human coronary artery occlusion is not certain.

I wish to thank Dr. M. Yen and Dr. R. C. Voss for their kind help.

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Electrocardiographic Changes Following the Administration of Hypertonic Saline to Dogs

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It was demonstrated previously that the administration of hypertonic saline to dogs may cause very marked circulatory and respiratory changes. The rapid intravenous injection of 1 ml. per kilogram of a 20 per cent solution of saline caused arrest of respiration, a marked rise in pulmonary venous and arterial pressures, either no change or a fall in left atrial pressure, and a marked decrease in systemic arterial pressure.[1] The pressure changes were attributed to spasm at the pulmonary venous-left atrial junction, apparently due to direct stimulation of chemoreceptors at this site, while the apnea was shown to be of reflex origin since it could be abolished by cervical vagotomy.

The circulatory and respiratory events following intravenous injection of hypertonic saline are accompanied by very pronounced electrocardiographic changes, which are the subject of the present report.

MATERIAL AND METHODS

Seven mongrel dogs, weighing between 6 and 14 kilograms, were anesthetized with thiopental sodium, 30 mg. per kilogram intraperitoneally, and with pentobarbital thereafter, as needed. Heparin, 30 to 50 mg., was given at the beginning of the experiment to prevent clotting. Right heart catheterization was performed in 3 dogs via the jugular vein. Systemic arterial pressure was obtained via a catheter introduced into the femoral artery. Pressures were measured by two electromanometers (Sanborn) and recorded, together with one or more leads of the electrocardiogram, on a four-channel direct writer. Respiration was recorded by a rubber chest pneumograph. In 2 dogs bilateral pneumothorax was produced and artificial respiration maintained by intermittent positive pressure, in order to exclude the reflex apnea which followed the injection. A total of 30 intravenous injections of 1 ml. per kilogram of a 20 per cent solution of saline was given to the 7 dogs, the duration of each injection being less than 10 seconds.

OBSERVATIONS

The electrocardiographic changes following the injection were similar in all experiments (e.g., Fig. 1). A transient, more or less pronounced, sinus brady-

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This study was supported by the Hadassah Medical Organization Research Fund.
Received for publication March 16, 1959.

cardia appeared in all cases within 5 seconds after the beginning of the injection, and was not prevented by premedication with 0.5 mg. of atropine. The effect of atropine was tested three times in one dog and twice in another; each time an injection of 0.5 mg. of atropine preceded the injection of hypertonic saline. The

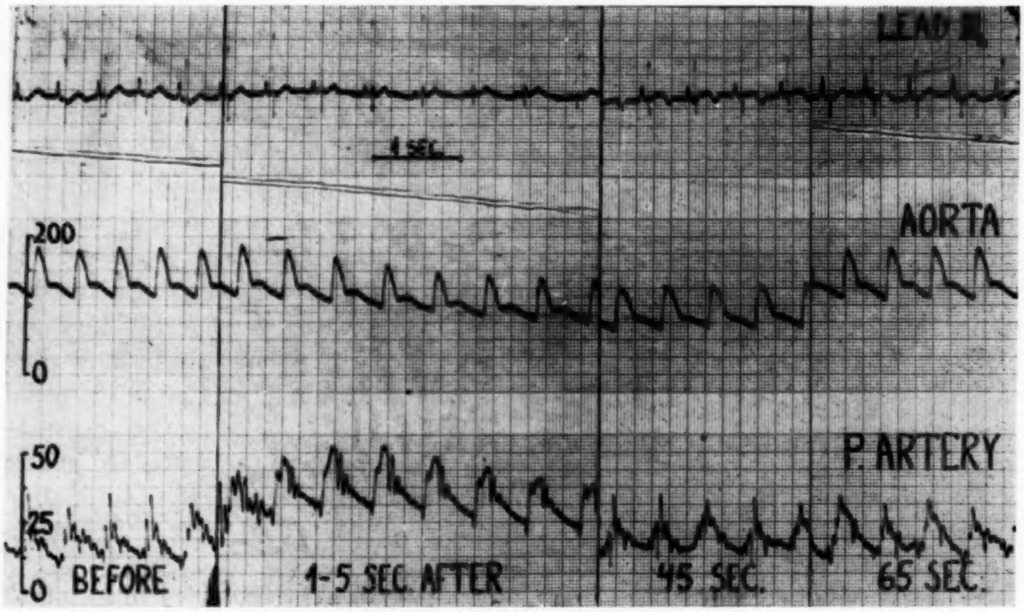

Fig. 1.—Effect of 1 ml. per kilogram of 20 per cent saline on the electrocardiogram of a dog. Note slight bradycardia, decrease in amplitude of P wave, shortening of P-Q interval, and increase in amplitude of QRS complex. These changes appeared immediately after the injection, at the time of pulmonary hypertension. Later, when they disappeared, the T wave became inverted.

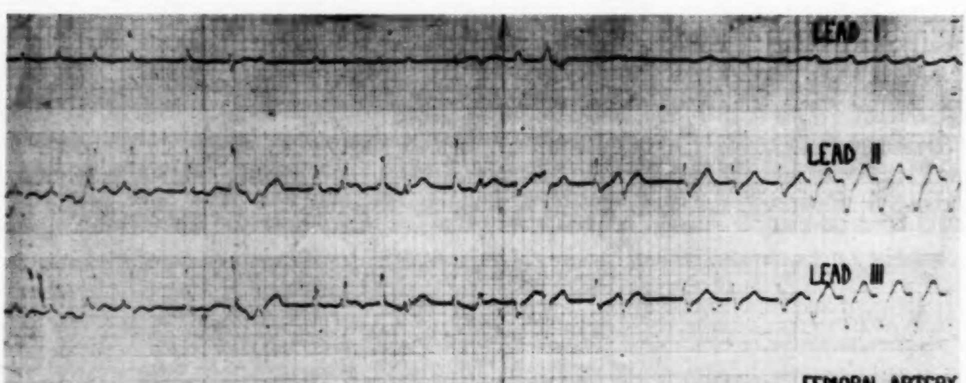

Fig. 2.—Effect of 1 ml. per kilogram of 20 per cent saline (third injection to this dog) on the electrocardiogram. Note appearance of multiple extrasystoles and ventricular tachycardia.

bradycardia was accompanied by a lowering of the voltage of the P wave, which also changed its shape and frequently became notched. The P-R interval either did not change or became shorter. At the same time the amplitude of the R wave in all leads increased markedly. The width of the QRS complex did not change, except after the administration of several injections to the same dog. Under these circumstances bundle branch block was sometimes observed. Ectopic atrial and/or ventricular premature beats from one or more foci were sometimes noted during the first 10 seconds after the injection. In one dog paroxysmal ventricular tachycardia appeared following the third injection of hypertonic saline (Fig. 2).

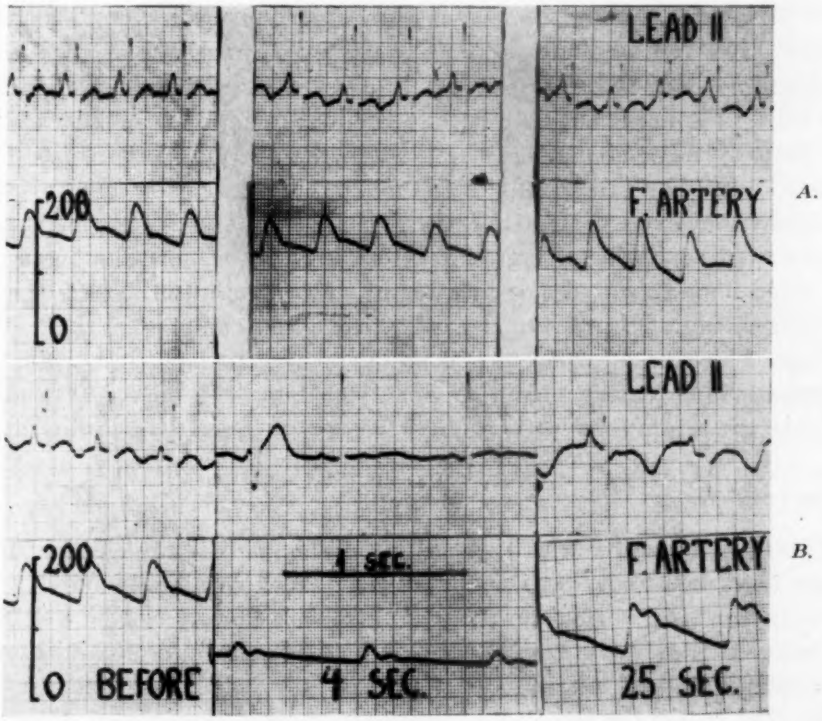

Fig. 3.—Effect of two subsequent injections of 1 ml. per kilogram of 20 per cent saline on the electrocardiogram and systemic arterial pressure. ***A*, First injection. Effect on pulse rate, P wave, and QRS complex is slight, and hypotension negligible.** ***B*, Second injection. Marked bradycardia, lowering of P wave, increase in amplitude of QRS complex, and an ectopic beat are seen; hypotension is very pronounced. Note very marked prolongation of Q-T segment and inversion of T wave.**

The changes mentioned above (except for the ventricular tachycardia) were transitory and disappeared within 20 to 40 seconds after the injection. They occurred simultaneously with the maximal rise of the pulmonary arterial pressure (Fig. 1) and the period of apnea. They did not seem to be caused by the fall of systemic arterial pressure, the lowest level of which was frequently reached after the described electrocardiographic changes had disappeared (Fig. 1). However, when the hypotensive effect of the hypertonic saline was more pronounced, the electrocardiographic changes were more prominent (Fig. 3). These early

changes were probably not dependent on respiration, because they were more or less similar whether there was apnea or whether the respiratory movements were maintained by mechanical means.

About 15 seconds after the beginning of the injection, when the electrocardiographic changes described above were fading or had disappeared, abnormalities in the S-T segment and the T wave appeared (Figs. 1-3). The Q-T interval invariably became longer because of prolongation of either the T wave or the S-T segment, or both. Sometimes, the S-T segment was either elevated or depressed. The T wave became flat, diphasic, or inverted in all experiments. U waves appeared very frequently, and sometimes became prominent or even huge. Changes in the S-T segment and T and U waves lasted from 1 to 2 minutes and were reversible after the first injection, but persisted longer or became irreversible after repeated injections.

Changes in the S-T segment and T and U waves seemed to be more related to the fall in systemic arterial pressure following the injection of the hypertonic saline than were the changes in the P wave and the QRS complex. The former appeared during, or subsequent to the maximal hypotension (Figs. 1, 3). There is no doubt, however, that although the changes in the S-T segment and T and U waves might have been aggravated by the hypotension, they were not caused by it, since they appeared also in cases in which the fall in arterial pressure was very insignificant (Fig. 3,*A*). In other cases the changes in the S-T segment and T and U waves returned to normal in spite of the fact that the arterial pressure remained low after the injection of hypertonic saline. Apnea seemed to aggravate the alterations in the final deflection of the electrocardiogram.

COMMENT

The mechanism by which hypertonic saline causes the electrocardiographic changes described above was not clarified. The role of Na^+ and K^+ and Ca^{++} in maintaining the normal activity of the heart muscle cell is well recognized. It is believed that the cationic gradient between the interior and exterior sides of the muscle cell membrane varies rhythmically with heart action.[2,3] During systole, Na^+ enters the cell and K^+ leaves it; during the recovery phase the initial gradient is restored. Ca^{++} is considered to be an antagonist of K^+.[4] It seems that both the constancy of the intra-extracellular gradient[2,3] and the absolute cellular ion content[5] are of extreme importance for the functioning of the heart muscle cell.

The electrocardiographic changes following the intravenous injection of hypertonic saline resemble those due to hypopotassemia and/or hypocalcemia. An increase in amplitude of the QRS complex, prolongation and depression of the S-T segment, inversion of the T wave, a prominent U wave, and arrhythmias are all typical of hypopotassemia.[6] Prolongation of the S-T segment and inversion of the T wave are observed during hypocalcemia.[7]

The intravenous infusion of a 5 per cent solution of saline, in doses sufficient to cause marked expansion of the extracellular fluid, has been shown to cause no significant change in the levels of serum potassium; nevertheless, slight

changes in the T wave and S-T segment have been observed in these cases.[8] No information is available about the changes in electrolytes following the injection of more hypertonic solutions, as in our case. Rapid intravenous infusions of 7.5 per cent sodium bicarbonate have been found to cause some discharge of potassium from the cells, a tendency to hypopotassemia, and an increased excretion of potassium in the urine.[9] Infusion of hypertonic sodium lactate also causes a fall of serum potassium and calcium.[10] This is accompanied by electrocardiographic changes different from those following the infusion of hypertonic saline, including an increase of pulse rate, abolition of extrasystoles, and narrowing of the QRS complexes, apparently related to an increase in pH of the blood. Hypertonic sodium succinate affects the electrocardiogram in a way very similar to that of hypertonic sodium lactate.[11] The pH of the blood, examined before and after the injection of hypertonic saline in several of our dogs, showed no change. Lengthening of the repolarization period of the frog ventricle under the influence of a high concentration of sodium in the perfusing fluid has been described.[12] Further experiments to elucidate the mechanism of the effect of hypertonic saline on the electrocardiogram are in progress.

SUMMARY

The effect of the rapid intravenous injection of 1 ml. per kilogram of a 20 per cent solution of saline on the electrocardiogram was examined in 7 anesthetized dogs. Bradycardia, decrease in amplitude and notching of the P wave, increased amplitude of the QRS complex, Q-T prolongation, and T-wave inversion were regularly observed. U waves, extrasystoles, bundle branch block, and ventricular tachycardia were sometimes observed as well. These changes were apparently influenced but not caused by the apnea and hypotension following the injection.

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Effects of Respiration on Transmission of Ballistocardiographic Forces From the Heart to the Recording System

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The effects of normal respiration on the main systolic (I-J) wave of the ballistocardiogram have been ascribed to respiratory variations in velocity and volume of blood ejected from the heart. Since I-J is larger in inspiration, and right ventricular ejection is greatest in inspiration, the assumption has been that right ventricular forces predominated over left. This could be ascribed to the statement, deduced from pulse pressure records,[1] that the right ventricular increase in ejection in inspiration is three to five times greater than the simultaneous decrease in left ventricular ejection. Recent data cast doubt on the original interpretation of the pulmonary arterial pressure curves, and hence on the widely accepted explanation for the ballistocardiographic phenomenon.

An additional factor in making pulmonary arterial events predominate in inscribing head-foot traces is the fact that the pulmonary artery is more closely parallel to the head-foot axis of the body than is the aorta. This is especially noteworthy in older people with a transverse position of the heart and a wide aortic arch. This gives a larger lateral component of force due to left ventricular ejection, especially in expiration when the heart is most transversely placed. Therefore, some decrease in head-foot force may be due to change in vector of left ventricular ejection during expiration.[2] This factor may be large in elderly subjects with a wide aortic arch, but it is often noted in those under 30 years of age.

During the past 4 years we have been observing the head-foot traces inscribed when the supine patient is tightly wedged between a platform with a shoulder yoke, to record from the cephalad part of the trunk, and one with a "bicycle seat," to record from the caudal part. Respiration causes much greater variation in the ischial than in the thoracic I-J wave. This makes it seem probable that respiration changes the transmission of forces from the generator in the heart and great vessels to the skeleton and the recording systems. Experi-

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This work was supported by Grant H-1250 from the Department of Health, Education and Welfare, Public Health Service, National Institutes of Health, Bethesda, Md.

Received for publication March 23, 1959.

ments designed to test this possibility indicate that inspiration, by tensing the mediastinal fibers, does increase transmission of force, and that this probably explains, in large part, the inspiratory increase in I-J waves.

METHODS

All observations were made on a single subject, selected because at the age of 60 years he has had a large respiratory variation in I-J size and shape for 10 years. He is a slender, relatively flat-chested subject, with the largest I-J waves in the head-foot plane, and smaller, less variable lateral and dorsoventral I-J waves, all increasing during inspiration.

A Sanborn Twin-Beam galvanometer was used to record the ballistocardiograms from platforms suspended on springs, with motion detected by an electromagnetic pickup, integrated by a condenser in parallel (resistance = 60,000 ohms, capacity = 1 microfarad). This resembles the device described elsewhere for obtaining lateral ballistocardiograms,[2] but the springs permit only head-foot motion, and there is a shoulder yoke, 5 cm. high in the center and 15 cm. on each side, at the upper end of the platform. The frame on which the platform is mounted rests on half-inch rollers, and is pulled footward by cords attached to each side of the frame and passing over pulleys to 14-pound weights hanging below the table. This gives a constant pressure on the shoulders, the trunk being restrained by a "bicycle seat" fitted against the ischia on a separate platform which is also mounted on springs attached to a frame firmly fastened to the table.

The brachial pulse was recorded with the Sanborn piezoelectric pickup, the respiration with a photoelectric cell recording the shadow of the abdominal wall through the D. C. amplifier of the Twin-Beam. Steady positive pressure was provided by a 100 1. Douglas bag, compressed by heavy weights to 16-18 cm. H_2O pressure. Positive pressure during inspiration was provided by a Bird respirator.

RESULTS

Valsalva Experiment.—The Valsalva experiment, with its recovery phase, is shown in Fig. 1, which begins with the first beat after the chest and abdomen have been fixed in maximal expiratory effort against a closed glottis. This is held until the muscles relax, full inspiratory position returning before the glottis is opened (after second systole in center strip), and normal respiration, with gradual return to normal mid-position, is resumed. The decrease in systolic force and in brachial pulse are gradual and almost the same in degree. When the maneuver is terminated the I-J wave reaches its maximal size on the first (Fig. 2) or second beat, as the chest expands to the inspiratory position, while the brachial pulse rises sharply on the third or fourth beat and reaches maximum much later, when the I-J waves in expiration are only half as large as those evoked by the first systoles of recovery.

The published curves of femoral and right ventricular pressure (Reference 1, Fig. 6) show a pattern of instantaneous return to normal right ventricular pressures when forced expiratory effort is relaxed. It therefore is possible to accept the ballistocardiographic pattern as being due to a very large initial stroke volume ejected by the right ventricle, with a rapid decrease so that when the first large ejection by the left ventricle occurs, the net effect is no greater than that of the first right ventricular ejection. But the published curves show large right ventricular systolic pressures still present after the large left ventricular ejections begin, and this after a period of strain much shorter than those preceding recovery in Figs. 1 and 2. The most likely explanation for the curves in Figs. 1

and 2 is that, as the chest returns from the full inspiratory position to normal, the large forces due to maximal ejection by the right and left ventricles are less fully transmitted to the trunk than the force of beats occurring when the mediastinum was drawn taut by the relaxation of expiratory effort, while systemic pulses and forces were still small.

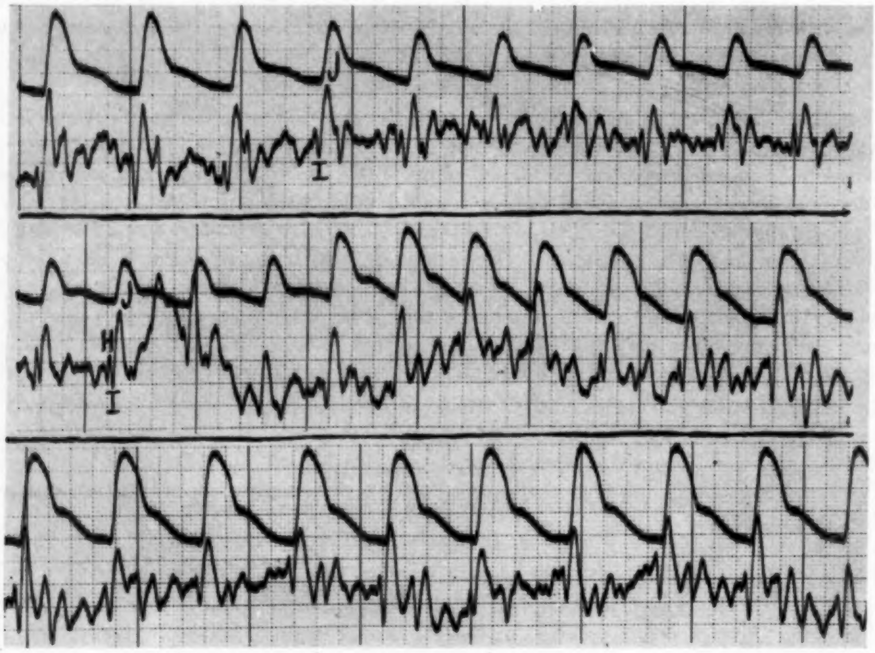

Fig. 1.—Effect of Valsalva experiment on brachial pulse (upper trace) and head-foot ballistocardiogram recorded from the thorax of a 60-year-old man. From a continuous record, 6 seconds omitted between each strip, with start at top, end in middle, and recovery at bottom. The pulse and I-J wave decrease gradually, but the delay in recovery of pulse is striking. Inspiration is rapid, and causes a sharp drop in the base line of the ballistocardiogram. Discussion in text.

Held Respiration.—The effects of held respiration, with the glottis open, are shown in Fig. 3. Pulse pressure, in many experiments such as this, regularly was largest in comfortably held, relaxed mid-position, and least in deep expiration with the abdominal wall maximally contracted. In deep inspiration, pulse pressure was high but the area under the systolic portion of the curve was less than in mid-position. The I-J wave regularly was small in mid-position, large in deep inspiration, and larger in straining expiration than in relaxed mid-position. In such records, made when a steady state has been brought about after 10 to 15 beats, the systemic pulse wave presumably is a good index of stroke volume of both ventricles. Such records provide striking evidence that the ballistocardiographic force recorded from the body is decreased when respiratory muscles relax, even if ventricular ejection is large.

Normal Respiration.—The records made during normal breathing also show a divergence between ballistocardiographic force and ventricular ejection. Studies made on dogs,[3] with indirect estimation of ventricular volumes from the areas

of the ventricles in cinematic records through windows, showed an inspiratory increase of 80 to 120 per cent in the right ventricular stroke volume, and expiratory increase of 70 to 85 per cent on the left. Calculations, from catheter studies of femoral and pulmonary pulse pressures and mean pressures, show that men usually have pulmonary arterial pulse pressures 50 per cent higher in inspiration than in expiration, but only 5 per cent greater systemic arterial pulse pressures during expiration than during inspiration (Reference 1, Fig. 18). But

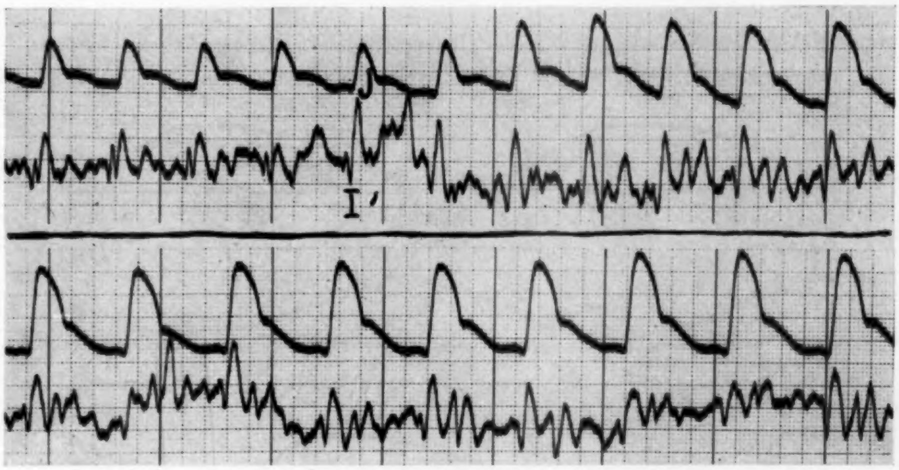

Fig. 2.—Continuous strips of end of Valsalva experiment, as in Fig. 1. Fifteen seconds of held inspiratory position preceded first beat. The first I-J wave after relaxing forced effort to exhale against closed glottis is large. It is 20 per cent larger than the last beat, during normal inspiration after recovery; the brachial pulse wave is 55 per cent smaller than in last beat.

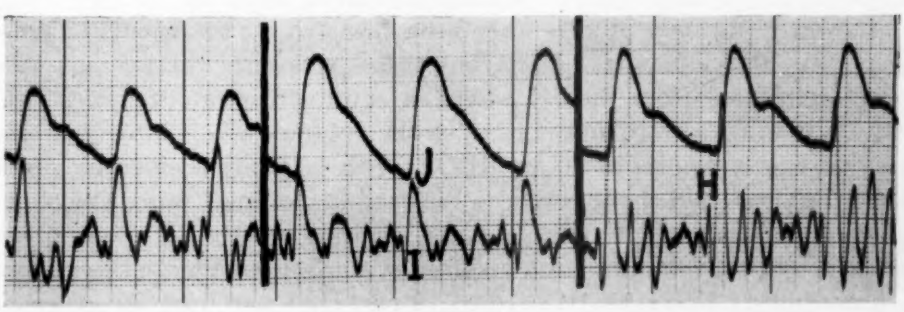

Fig. 3.—Brachial pulse, above, and head-foot ballistocardiogram, below. On left, during straining in full expiration; on right, full inspiration; center, relaxed mid-position. All with open glottis, starting 10 to 12 seconds after the respiratory position was held. The largest pulse waves and smallest I-J waves are seen in mid-position.

both dogs and men have a steady rise and fall, with maximal and minimal changes at the end of each respiratory phase. Such curves, and those in catheter studies of pulmonary arterial pressure in patients at the Kings County Hospital, all show gradual decrease in pulse pressure throughout expiration. This is in striking contrast to ballistocardiographic curves (Figs. 4 and 5). These show a gradual

increase during inspiration, with a sharp fall early in expiration. Studies of action currents in the phrenic nerve[4] show that the diaphragm normally relaxes completely at the start of expiration, no action currents being recorded after the onset of this phase. The change in intrathoracic pressure and right atrial filling is progressive as the relaxed diaphragm moves upward, but diaphragmatic tension drops precipitously, and the size of recorded I-J waves also drops so fast that the earliest I-J wave in expiration often is the smallest in each respiratory cycle.

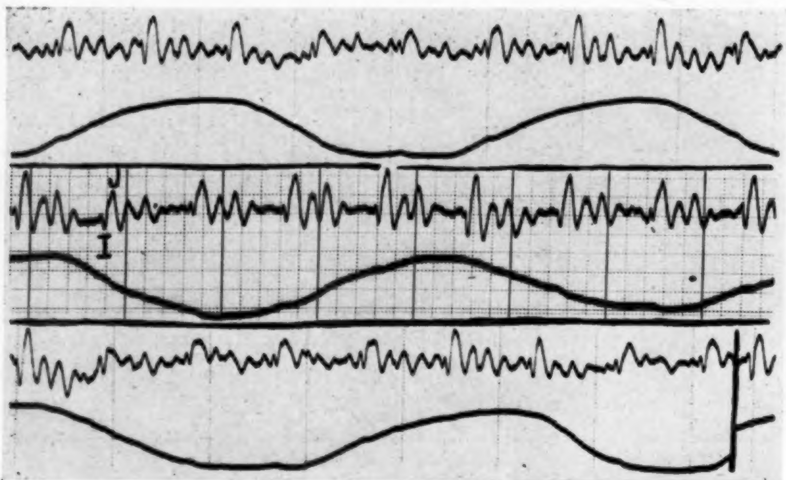

Fig. 4.—Respiratory motion of abdominal wall, with inspiration upward, and head-foot ballistocardiogram during quiet breathing. The smallest I-J wave in each respiratory cycle occurs at start of expiration. Black bar at end of lower strip shows 1 second omitted.

Pressure Breathing.—Studies have been reported on the effects of pressure breathing on the ballistocardiogram, but these gave only the average "stroke volumes" calculated from the I-J waves in several respiratory cycles.[5] They showed a rise in pulse rate and fall in "stroke volume" when subjects breathed against constant pressures of 30 cm. H_2O. With inspiration aided by pressure, a fall in pulse rate, and slight rise or fall in "stroke volume" was deduced, using maximal pressures of 25 cm. at the end of inspiration. No data were given on the effect of pressure breathing on respiratory variation. Our subject repeated these procedures. However, only 16 to 18 cm. H_2O was used for experiments with constant pressure, since it was found that abdominal muscles contracted and an expiratory position was favored when the subject breathed against pressures over 20 cm. H_2O.

As shown in Fig. 6, the brachial pulse pressure fell, the heart rate rose, and the I-J waves were larger, especially during expiration, when breathing against 16 cm. H_2O pressure. With the Bird respirator, the trained subject has short, swift expiration, and slow inspiration, so that in the control without the respirator an attempt was made to simulate this, with a full inspiratory position. As shown in Fig. 7, this causes a single small I-J wave in each expiration, with four or five

rather large waves in inspiration. The pressure-aided inspiration causes a faster rate, with smaller pulse pressures, and slightly larger I-J waves, especially the ones in expiration. These experiments confirm the well-established fact that venous return and minute volume flow are reduced by either type of pressure breathing. They show that when the deep inspiratory position is reached in each breath, the I-J waves of the ballistocardiogram are not diminished by levels of intrapulmonary pressure which reduce cardiac output. Here there is clear evidence that the inspiratory position increases the recorded force of the systolic waves of the ballistocardiogram even though intrathoracic pressure is prevented from falling and venous return is reduced rather than increased during inspiration with positive intrapulmonary pressures.

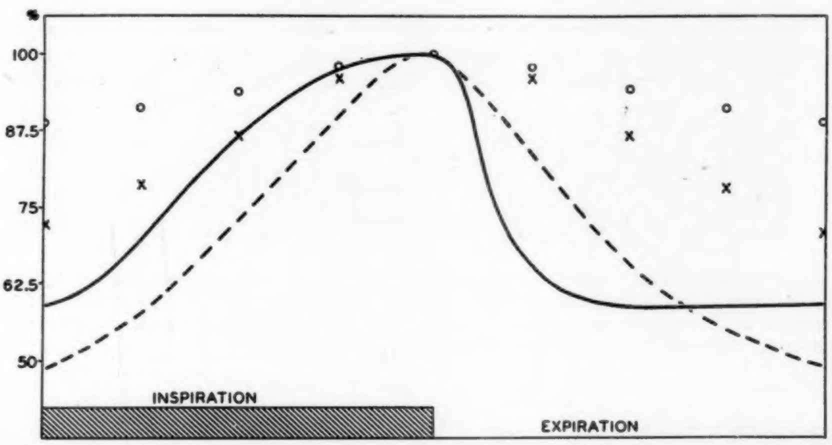

Fig. 5.—The solid line shows respiratory variation in thoracic head-foot I-J wave in 25 respiratory cycles, normal breathing (as in Fig. 4). The dashed line is the right ventricular stroke volume of a dog (Reference 2, Fig. 3). The crosses are the stroke volumes of the right ventricle of a man (Reference 1, Fig. 18), given by equation SV = K PP applied to pulmonary arterial pressure curves. The open circles give stroke volumes if equation SV = K PP/Log_{10} MP is applied. All values are given as per cent of maximum in inspiration. Note the very sharp early expiratory fall in I-J amplitude, and gradual expiratory decrease in stroke volumes.

Force Transmission in a Model "Mediastinum."—An artificial mediastinum was constructed by mounting a 1.5 by 3.5-cm. wooden beam, 18 cm. long, 12.5 cm. above the center of the recording platform. It was rigidly fastened to an upright beam securely attached to the platform at the "head" end. A sheet of woolen cloth was hung over the longitudinal beam, and a 250-gram iron pipe, 15 cm. long, was attached halfway between beam and platform. A cord, attached either to the beam or to the pipe, was given repeated tugs by a 50-gram weight falling 2 cm. before taking up the slack in the cord. As shown in Fig. 8, when the cloth "mediastinum" hangs loose, the "I-J" wave is 40 per cent as large, and the natural frequency of the initial waves is half as great, as when the cloth is tightly held to beam and platform. Transmission of force is 90 per cent effective when the "mediastinum" is taut, and 35 per cent effective when it is loose. Doubling the weight when the "mediastinum" is taut reduces transmission of force to 78 per cent, from 90 per cent, and slightly decreases natural

frequency of the entire system, which includes the platform and the tensing device. These crude tests indicate that there may be a considerable loss of energy between the heart and great vessels when, in expiration, the entire weight of mediastinal viscera hangs loosely from the sternum, and better transmission when, in inspiration, the mediastinum is tensed by diaphragmatic descent and sternal elevation.

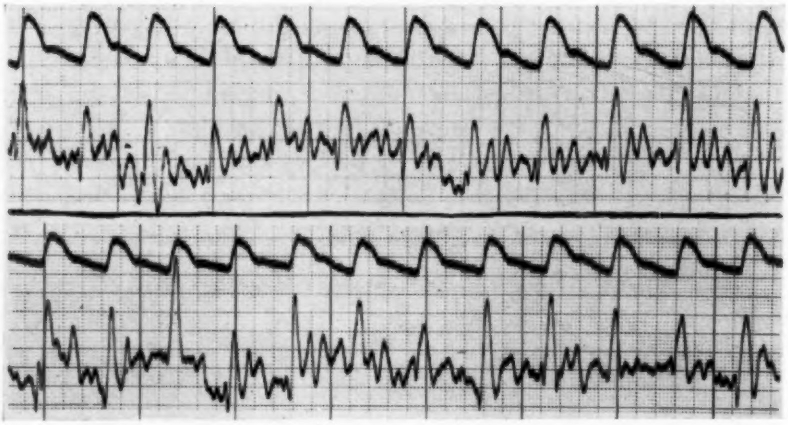

Fig. 6.—The upper strip shows brachial pulse and head-foot ballistocardiogram during breathing near the full inspiratory position; lower strip, during respiration against constant pressure of 18 cm. H_2O. Pressure in the trachea raised the pulse rate 5 per cent, reduced the average systemic pulse pressure 23 per cent, and raised the I-J waves 18 per cent.

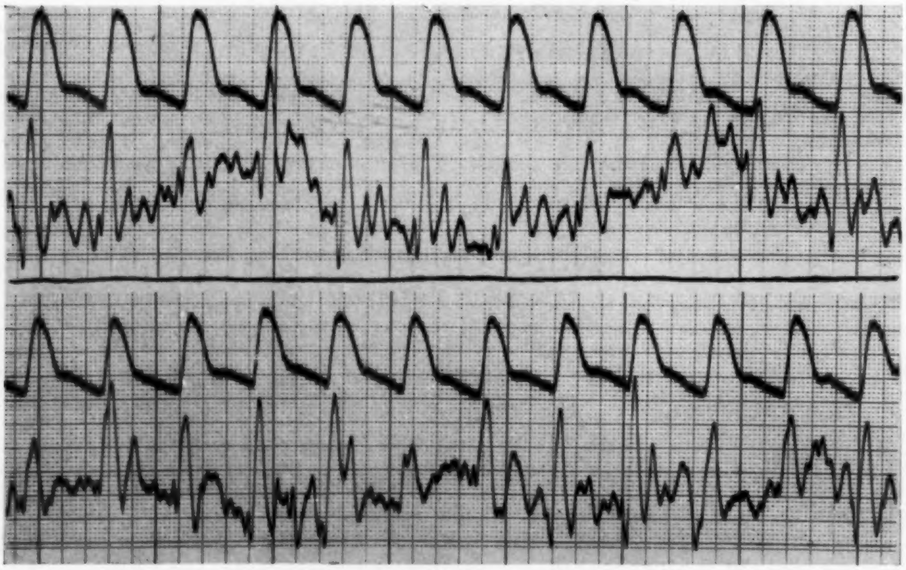

Fig. 7.—The upper strip shows brachial pulse and head-foot ballistocardiogram with slow, deep inspiration and rapid expiration, during which the base line of the ballistocardiogram rises sharply. The lower strip shows similar cycles, but with positive pressure rising to 25 cm. H_2O during inspiration and falling swiftly on expiration to atmospheric pressure (Bird respirator). Inspiratory positive pressure raised the pulse rate 7 per cent, and the average I-J wave 11 per cent, but lowered the pulse pressure 20 per cent.

DISCUSSION

From the earliest observers to the most recent reviewers, the respiratory variation of the I-J wave, and the exaggeration of this variation in the aged and in heart disease, has been accepted as being due entirely to variations in the forces generated by systolic contraction. On the basis of the classic paper of Lauson, Bloomfield and Cournand, it was possible after 1946, to make out a fairly convincing argument in support of the currently accepted view of the great respiratory variation in I-J amplitude, for these pioneers in cardiac catheterization had interpreted the pulmonary arterial pulse curves (Reference 1, Fig. 18) as showing that right ventricular stroke volume normally increased up to 50 per cent during inspiration. The conclusion that inspiratory difference in total ejection was +36 per cent was only qualified by saying that "it is not unlikely it may actually be greater" (Reference 1, Fig. 18, legend). Since I-J amplitude varies as the square of stroke volume, this seemed to explain the observed facts.

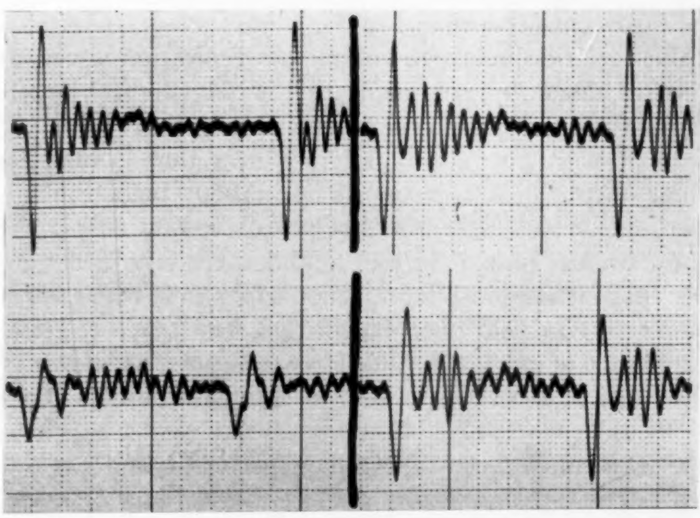

Fig. 8.—The response of the ballistocardiographic recording system to the tug produced by a 50-gram weight falling 2 cm. Upper left, tug directly on artificial "sternum" (see text); upper right, tug on 250-gram mass in taut cloth "mediastinum"; lower right, on a 500-gram mass in taut "mediastinum"; lower left, in a 250-gram mass in lax "mediastinum." Discussion in text.

This interpretation of the curves was based on the belief that pulmonary pulse pressures were directly proportional to stroke volume. It had long been known[6] that stroke volume in the aorta was proportional to pulse pressure divided by mean pressure. No such correction was applied to the pulmonary arterial pulse curves, which showed a rise of 43 per cent in mean pressure and a rise of 36 per cent in pulse pressure on inspiration. If the formula derived from studies of flow and pressure in the systemic circulation had been used, it would have been concluded that right ventricular stroke volume fell during inspiration. Work on dogs[3] had indicated a very large increase in right ventricular ejection during inspiration, and it was obvious that the equation which fitted ejection

into the thick-walled aorta could not be used for the pulmonary artery. Therefore, no correction for mean pressure was used.

Fritts and Cournand have recently published data on the cardiac index and on mean pressure and pulse pressure in the pulmonary artery of normal subjects during hypoxia or acetylcholine infusion (Reference 7, Figs. 2 and 3). From these data it is evident that the change in stroke volume, when mean pressure varies, is not directly related to change in pulse pressure, and that the equation

$$SV = K\frac{PP}{MP}$$

does not fit the data either. There is a rather good fit using the equation

$$SV = K\ \frac{PP}{\text{Log}_{10}\ MP}$$

When this is applied to the original data on respiration and pulmonary pulse pressure, it is found that the increase in stroke volume on inspiration is not 36 per cent, but 12 per cent (as seen in Fig. 5).

In dogs[3] the variation in stroke volume on respiration is very large, but the rise in right ventricular output on inspiration is only slightly larger than that in left ventricular output on expiration. When pulmonary pulse pressure is corrected for mean pressure changes, it becomes clear that in man also the rise in right ventricular output on inspiration is only about twice the fall in left ventricular output, the net change probably not exceeding 10 per cent in normal breathing, and often less than 5 per cent. This is entirely inadequate to account for the 100 per cent increase in I-J amplitude which may occur during inspiration in normal subjects. On held deep inspiration, resistance to flow through the pulmonary capillaries is increased,[8] and stroke volume, as shown in Fig. 3, may be less than in held mid-position. Yet, in this situation the I-J wave is very large.

The other experiments, on Valsalva experiment and pressure breathing, and the sharp fall in I-J amplitude in the earliest beats of normal breathing, all can be explained if transmission of ballistic forces to the trunk is impaired when the mediastinum is lax, during expiration, and is more effective during inspiration, becoming maximal at deep inspiration even when pressure breathing reduces venous return and stroke volume of both ventricles. The experiments with a crude model of the mediastinum illustrate that such impairment of transmission of force may occur, but only by careful study on cadavers can the reality and quantitative significance of such a factor be established.

Transmission of head-foot and lateral forces to the skeleton should be most sensitive to respiratory changes in fiber tension, but the pull of dorsoventral forces on the sternum should be little affected, since these are tensed, in the plane in which force is applied, by the weight of the heart and great vessels. The changes should be greater in aged people and those with deep chests than in those with youthful resilience in the connective tissue, and with relatively short sternovertebral diameters. The values obtained by March[9] seem in agreement with this reasoning. Mean inspiratory I-J divided by mean expiratory I-J gave

in the head-foot trace 1.32 in men under 30 years old, 2.5 in men over 50 years old, 1.28 in women under 30 years old, and 1.63 in women over 50 years old. The dorsoventral traces gave 1.22 for young men, 1.17 for old men, 1.37 for young women, and 1.17 for old women. Since the pulmonary outflow tract, as seen in lateral angiocardiograms, has a much larger front-back slope than the aortic outflow, it would be expected that inspiratory increase in I-J amplitude, if it were due chiefly to the excess of right over left ventricular ejection forces, would be greater in the dorsoventral plane than in the head-foot plane. The fact that the reverse is true can best be accounted for by a relatively high efficiency of transmission of dorsoventral forces even in expiration.

The experiments of Starr and Friedland[10] on respiration and the ballistocardiogram led them to conclude that changes in stroke volume were the basis of all observed variation in I-J amplitude. They tested for possible effects of change in vector as the apex of the heart rose in expiration, and used a type of pressure breathing which at times produced a sharp rise and fall in tracheal pressure, and at other times a sharp rise followed by a slow rise throughout inspiration. In one experiment, on a man with ventricular aneurysm, pressure was applied uniformly after the chest reached full inspiration, and the chest volume decreased slightly as the pressure rose. It is safe to conclude from these experiments that venous return and stroke volume, as affected by intrathoracic pressure, may often explain the changes in I-J amplitude noted in respiration.

As in most young people, the respiratory variation in S.H. (Reference 10, Fig. 3) is small, as it is in H.H., a young woman with decerebrate rigidity. H.H. showed a marked increase in the size of H and a slight decrease in I-J when a blast of oxygen was directed into her tracheal catheter. But in a normal 50-year-old man, Starr and Friedland record exactly what is seen in the experiments now reported. In Fig. 1 of their paper, as in Fig. 4 here, the first beat in expiration of I.S. is the smallest, with a progressive rise in later beats. Pressure breathing in I.S. gave larger I-J waves when the chest volume was large than when it was small and the intrathoracic pressure was low, presumably with better cardiac filling. In their subject C.F. (Reference 10, Fig. 1, third row) the first two beats after the start of high pressure, but with little change in chest volume, show small, notched I-J waves. When the pressure and chest volume increase, the I-J form returns to normal and the size increases. Filling of both ventricles must have been progressively decreasing. Thus, the actual figures in some of the classic experiments of Starr and Friedland seem to be best explained by a relation between chest volume and I-J height, although a relation to stroke volume, when chest volume changes little or very slowly, is quite evident.

Even if it should be proved that the striking respiratory variation in I-J amplitude of older men is due largely to altered transmission of systolic forces to the body and the recording system, the reported correlations of ballistocardiographic patterns with physiologic, pharmacologic, and pathologic influences on the circulation will remain unchanged. The explanation for these correlations may then be based more soundly than in the past.

CONCLUSIONS

A re-examination of published data on respiratory variation in the output of both ventricles indicates that output of the right ventricle varies much less, in relation to that of the left ventricle, than had been believed when current explanations of the large respiratory increase in the systolic waves of the ballistocardiogram were proposed. The total stroke volume probably does not increase more than 10 per cent, while an increase of 100 per cent in the I-J wave is accepted as normal.

Studies of brachial pulse waves and ballistocardiograms during various respiratory maneuvers indicate that the I-J amplitude may increase markedly on inspiration even when stroke volume ejection is relatively small.

A model "mediastinum" shows that the force transmitted from a mass in its center may decrease more than 50 per cent when the mass hangs from the "sternum," as compared with that transmitted when the "mediastinum" is tensely fastened to the "spine."

It is concluded that most of the respiratory variation in the I-J waves of the ballistocardiogram is due to variations in transmission, rather than in generation, of force.

Reasons are given for believing that respiration will have little effect on transmission of dorsoventral forces, which actually have been noted to increase only 17 per cent during inspiration in the ballistocardiograms of elderly men, while head-foot I-J increased 150 per cent in the same cycles.[9]

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Case Report

Familial Cardiomegaly in Association With the Wolff-Parkinson-White Syndrome

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The authors have recently encountered two siblings with the typical features of familial cardiomegaly and the Wolff-Parkinson-White (WPW) electrocardiographic pattern. The third sibling, an 18-year-old boy, is reported to be in good health. The father, aged 46, and the mother, aged 45, are also asymptomatic.

CASE REPORTS

CASE 1.—P. D., a 13-year-old girl, was referred to the University of Minnesota Hospitals for cardiac evaluation in 1958. No cardiac symptoms or findings had been noted in early childhood. At the age of 10 years she was examined because of abdominal pain, and the consulting physician noted a cardiac murmur. An electrocardiogram showed occasional premature systoles and S-T segment changes, with negative T waves in Leads I, V_5, and V_6. The roentgenogram showed mild cardiomegaly.

When evaluated at this medical center, she appeared healthy and was entirely asymptomatic. The blood pressure in the right arm was 112/56 mm. Hg. No cardiac thrills were noted. The cardiac apex was displaced slightly to the left of the mid-clavicular line in the sixth intercostal space. A Grade 2 to 3 systolic murmur of medium pitch was heard along the left sternal border and out to the apex. A variable apical diastolic third heart sound, but no distinct diastolic murmur, was also noted. The second sound was split, of normal intensity, and loudest in the second left intercostal space. No neurological abnormalities were noted. Cardiac enlargement, involving primarily the left ventricle, was noted on the chest roentgenogram (Fig. 1). The left atrium and pulmonary vasculature appeared normal. The electrocardiogram now showed the WPW pattern (Fig. 2).

At the present time she continues to be asymptomatic and has had no known bouts of paroxysmal tachycardia.

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Supported by funds from the U. S. Public Health Service and the Minnesota Heart Association.
Received for publication March 31, 1959.

CASE 2.—M. D., the male sibling of Patient P. D., was noted to have a heart murmur at the age of 8 years. He had had no cardiac symptoms, but was being treated by a psychiatrist for "nervousness." At the age of 14 years he experienced dizziness and syncope while hiking. Cardiac evaluation at this time at the University Hospitals revealed definite cardiomegaly and a widely transmitted systolic murmur that was maximal in the second right intercostal space. The electrocardiogram showed a typical WPW pattern (Fig. 3). Moderate cardiomegaly was evident on the chest roentgenogram (Fig. 4,*A*).

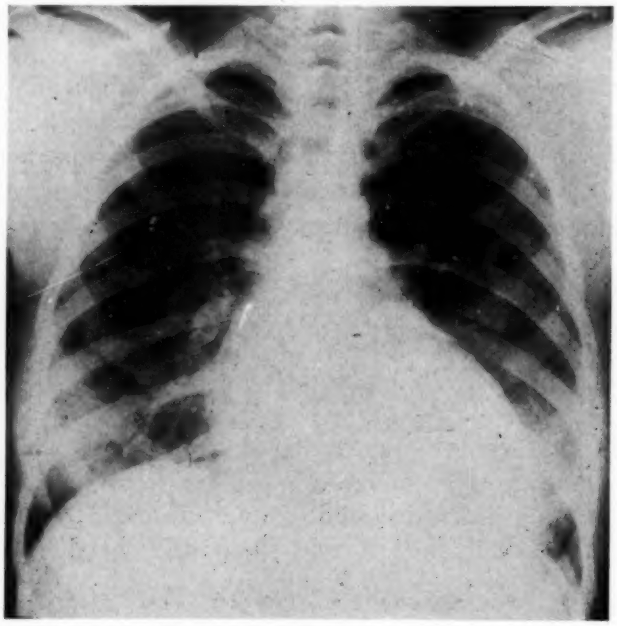


Fig. 1.—Roentgenogram of Patient P. D., showing moderate cardiomegaly and normal pulmonary vasculature. This 13-year-old girl has the WPW syndrome and familial cardiomegaly, but is presently asymptomatic.

The boy remained relatively asymptomatic until the age of 15 years. At this time, while on a camping trip, he suffered smoke inhalation when his sleeping bag caught fire. Several days later he noted exertional dyspnea, followed by pain and a "tightness" in the epigastrium and retrosternal area. These symptoms were relieved by vomiting. Similar symptoms occurred almost daily, often associated with severe nausea and vomiting. Several months after the incident of smoke inhalation he developed cardiac failure. This responded well to a program of salt restriction, digitalis, and diuretics. No specific diagnosis other than idiopathic myocarditis was made at this time.

He was admitted to the University of Minnesota Hospitals shortly thereafter for right heart catheterization. He acknowledged that he had been having occasional episodes of palpitation. He appeared asthenic at this time, but was comfortable at rest. The blood pressure in the arm was 120/65 mm. Hg, and the heart rate was 76 per minute and regular. A precordial bulge was noted. The apical impulse was located in the sixth left intercostal space in the anterior axillary line. There was a harsh systolic murmur at the apex and along the left sternal border, and a soft blowing diastolic murmur in the left mid-clavicular line. The second heart sound was accentuated and widely split in the second left intercostal space. The liver was palpable, with evident enlargement. Roentgenograms taken during this hospitalization showed further cardiac enlargement as well as increasing pulmonary congestion (Fig. 4,*B*). The electrocardiogram again showed the WPW pattern.

At cardiac catheterization, the pulmonary artery could not be entered. Right ventricular pressure was 50/13 mm. Hg. There was no evidence of a left-to-right shunt, and the arterial oxygen saturation was 92 per cent. Vital capacity was 2.6 liters. The administration of Decholin to determine the circulation time precipitated temporary shock.

Within several months the patient developed intractable congestive failure accompanied by severe nausea, vomiting, retching, and restlessness. The terminal episode was characterized by marked air hunger, tachypnea, and profuse cold perspiring.

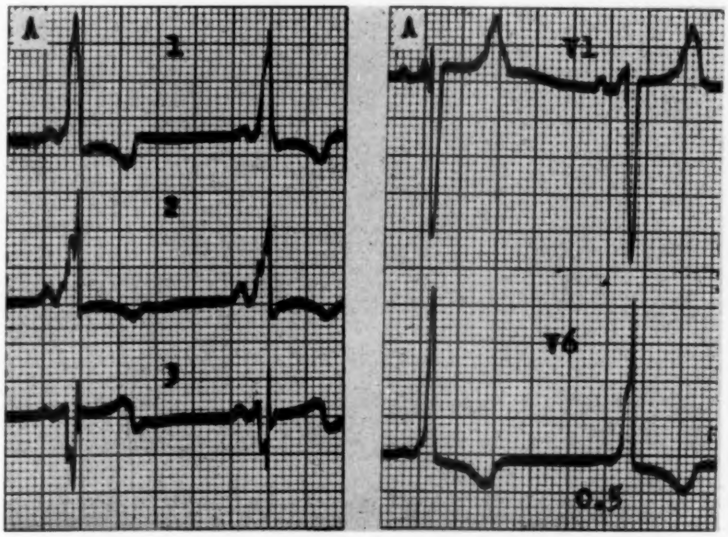


Fig. 2.—Electrocardiogram of Patient P. D., showing WPW pattern of Type B (simulating left bundle branch block). Leads I, II, and III were taken simultaneously, as were Leads V_1 and V_6. Note the different configurations of the delta wave (the initial slur of the QRS complex) in the various leads.

At autopsy,* the pertinent findings were limited to the cardiovascular system. The pericardial sac was widely dilated and contained 75 c.c. of fluid. The heart weighed 1,000 grams. Three right pulmonary veins entered the left atrium. The middle one was small and entered near the superior vena cava. There were no other anomalies of the great vessels. The ductus arteriosus was short and obliterated. The surface of the heart was of a pale gray-brown color, with scattered grayish areas over both ventricular surfaces. Under these areas the myocardium appeared thin by palpation. All of the valves appeared normal. There was some dilatation of the pulmonary conus, and some prominence of the obturator band in the right ventricle. On section, the myocardium showed irregularly shaped, mottled gray, firm areas and red-to-brown softer areas. The aorta and coronary arteries were of normal size and free of sclerosis. The pulmonary vessels likewise were normal in appearance. The liver weighed 2,150 grams, and the spleen, 265 grams. The peribronchial, periaortic, and hilar lymph nodes were markedly enlarged. The gross anatomic diagnoses were: (1) cardiac hypertrophy, (2) myocardial fibrosis, (3) ascites, (4) right pleural effusion, (5) chronic passive congestion of the lungs, liver, and kidneys, and (6) lymphadenopathy. Microscopic examination of multiple sections from all areas of the heart showed a consistent picture. There was marked scarring of the myocardium, with many large and small areas of dense fibrous connective tissue replacing the muscle cells. These scars were moderately vascular and generally sparsely cellular. However, there were a few dense focal collections of lymphocytes in these scars. The muscle cells between the scarred areas were extremely large, with large nuclei. At the periphery of these scars there were numerous large muscle

*Performed by Dr. Kano Ikeda, Miller Hospital, St. Paul, Minn.

cells having a somewhat irregular shape, a moderately basophilic cytoplasm, and very large, irregularly shaped hyperchromatic nuclei. The pericardium, endocardium, and valve leaflets did not appear to be involved in the scarring. A representative area is reproduced in Fig. 5. Special stains for glycogen were not done.

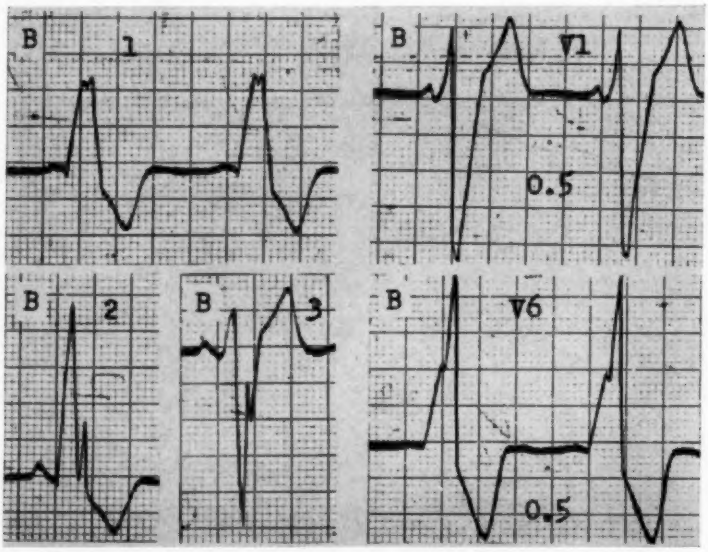


Fig. 3.—Electrocardiogram of Patient M. D., also showing Type-B WPW pattern with very wide QRS complexes and marked T-wave aberrations. This boy died of severe congestive failure at the age of 16 years. Necropsy showed widespread myocardial fibrosis.

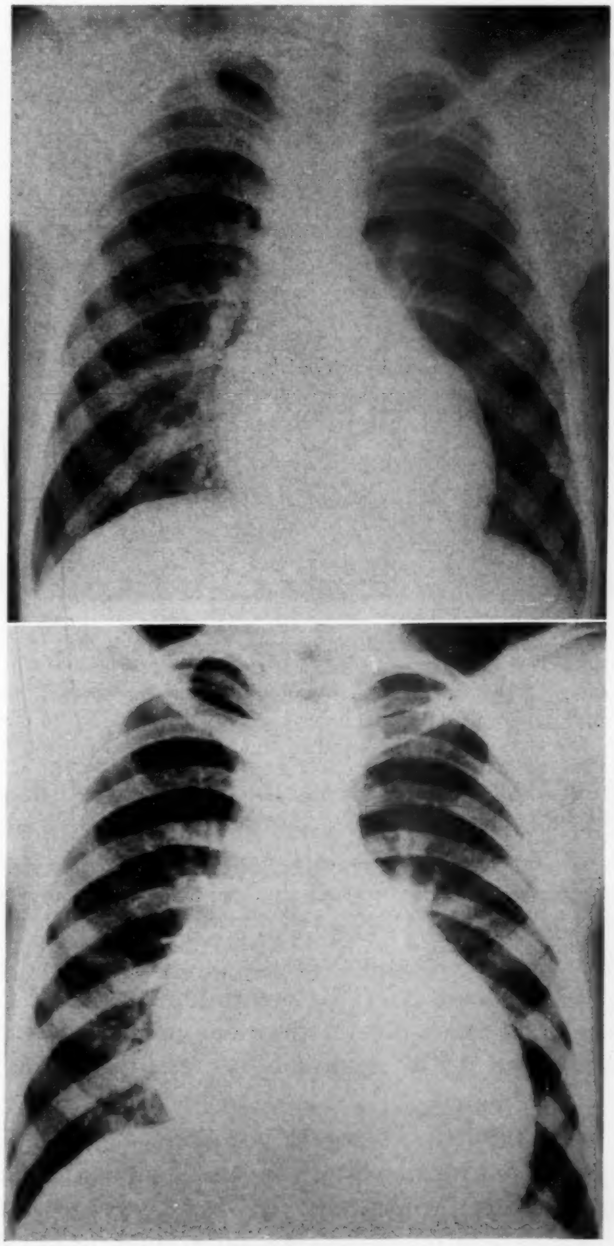
DISCUSSION

The term "familial cardiomegaly" was first employed by Evans,[1] in 1949, to describe nine cases with cardiomegaly of unknown etiology. Three cases occurred in one family, two in another family, and the other four were sporadic cases. All nine patients had a similar clinical picture. Cardiomegaly was frequently first noted on a routine chest roentgenogram. Usually, there were few or no symptoms until adult life. When symptoms eventually occurred, they consisted of palpitations, dizziness, syncope, and Adams-Stokes attacks. Death occurred during these attacks or from congestive failure precipitated by various arrhythmias.

The physical examination usually showed a normal blood pressure, cardiomegaly, and an irregular pulse. The heart sounds were clear, but there was usually either prominent splitting of the second sound in the pulmonary area, or a "triple rhythm" at the apex from the addition of a third heart sound.

Roentgenograms showed marked cardiac enlargement involving primarily the left ventricle, although in several cases the right border of the heart was also prominent. Evidence of pulmonary venous congestion was often present. The electrocardiograms showed premature systoles, paroxysmal auricular tachycardia, auricular flutter or fibrillation, varying degrees of atrioventricular and bundle branch block, and numerous changes in the S-T segment and T wave.

Four of these nine patients died, usually within a few months or years after the onset of their symptoms. A detailed necropsy in one case showed interstitial fibrosis of the myocardium, with marked hypertrophy of the remaining muscle fibers. There was no gross cellular infiltration or fatty replacement of the muscle fibers. In this same case, greater than usual amounts of glycogen were found



A.

B.

Fig. 4.—Roentgenograms of Patient M. D. *A*, Sept. 4, 1951. Note moderate cardiomegaly and normal pulmonary vasculature. Age 13 years. *B*, Jan. 6, 1954. Note increased cardiomegaly and pulmonary vascular congestion. Death occurred 3 months later at age 16 years.

in the remaining cardiac muscle fibers and in the vastus externus muscle, but there was no evidence of glycogen storage disease.

Among the many cases of familial cardiomegaly in the literature, there are several that have been noted to have the WPW electrocardiographic pattern. In Evans' original article[1] the electrocardiogram of Case 8 appears to show the WPW syndrome.

Fig. 5.—Photomicrograph (×120) of section of heart of Patient M. D. Note marked scarring of the myocardium, without evidence of inflammation or necrosis. The muscle cells between the scarred areas are extremely large with large nuclei. (Courtesy of Dr. Kano Ikeda, Miller Hospital, St. Paul, Minn.)

Cases of familial cardiomegaly with the WPW pattern have been reported by Campbell and Turner-Warwick[2] (Case 4), and by Soulié and his associates[3] (Cases 2 and 4). Case 1 in Soulié's paper[3] also appears to have the WPW syndrome, since on one occasion (prior to auricular fibrillation) the electrocardiogram had a P-R interval of 0.08 second and a QRS duration of 0.12 second. Interestingly enough, Soulié's family was also afflicted with Weber-Osler-Rendu disease (familial telangiectasia). This association of the WPW pattern with familial cardiomegaly is much greater than one might expect from coincidence alone. Incidentally, the WPW syndrome by itself may show a familial tendency.[4-6]

The cause of familial cardiomegaly is unknown. Campbell and Turner-Warwick[2] have suggested an hereditary factor (dominant gene). Others have viewed it as myocardial toxoplasmosis, glycogen storage disease, progressive muscular dystrophy without muscular impairment, or Friedreich's ataxia without neurological manifestations.

The authors have seen the WPW electrocardiographic pattern in a child with marked neurological findings (mental retardation, optic atrophy, seizures,

hyperactive deep tendon reflexes), possibly representing a variant of Friedreich's ataxia.[4,5] This 9-year-old boy died in severe congestive failure. Necropsy showed diffuse myocardial fibrosis and an increased amount of glycogen in the remaining myocardial fibers. Whether familial cardiomegaly is an etiologically distinct entity or whether it represents an already known disease with cardiac manifestations in some individuals, primarily neurological manifestations in others, and both cardiac and neurological manifestations in the remainder, remains to be established.

The sporadic case of familial cardiomegaly (i.e., wherein only one member of a family has the myocardial involvement) is at present an exclusion diagnosis based on the clinical picture as formulated by Evans.[1] When such a sporadic case of familial cardiomegaly occurs with the WPW pattern, the differentiation from Ebstein's anomaly of the tricuspid valve may be difficult, particularly since the WPW pattern is also frequently seen in this latter anomaly.[5,7,8] The roentgenogram is useful in differentiating these two entities. Either pulmonary congestion or normal pulmonary vasculature occurs in cases of cardiomegaly due to familial cardiomegaly, while in Ebstein's anomaly with comparable cardiomegaly the pulmonary vasculature is almost always lower normal or decreased. Differentation during life may require cardiac catheterization with the intracavitary electrode catheter.[7,9,10]

SUMMARY

Two cases of familial cardiomegaly in association with the WPW syndrome are recorded. The male sibling died of severe congestive failure at the age of 16 years. Necropsy showed a huge heart weighing 1,000 grams and widespread myocardial fibrosis. His 13-year-old sister has cardiomegaly, but is presently asymptomatic.

Other cases of familial cardiomegaly with the WPW syndrome are noted. The etiology of this disease is unknown. The difficulty of differentiating an isolated case of familial cardiomegaly with the WPW syndrome and Ebstein's anomaly of the tricuspid valve is briefly discussed.

The authors are grateful to Dr. Kano Ikeda, Pathologist, Miller Hospital, St. Paul, Minn., for the use of his case material in the preparation of this manuscript. We also wish to thank Dr. Barbara Burke and Dr. James Dawson, of the Department of Pathology, University of Minnesota, Minneapolis, Minn., for their valuable aid and advice.

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Review

The Management of Angina Pectoris

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The original description of angina pectoris by Heberden[20] in 1768, published in 1772, remains undisputedly authoritative; in two centuries nothing has been withdrawn from it and but little has been added. However, the physiopathologic significance of this "symptom-complex," at first admirably divined, subsequently underwent curious misinterpretations. Even at the present time, too many physicians think that angina is the expression of an "aortitis." Nevertheless, since the work of Keefer and Resnick,[23] it seems unanimously agreed that angina is the painful manifestation of ischemia of the heart, the subjective reflection of the hypoxia of the myocardial cells. Whether the myocardial pain is a direct result of an insufficient oxygen tension in the cardiac tissues, or is induced by an insufficient elimination of metabolic products by an inadequate blood flow is certainly a question of importance; but the basic concept remains—namely, that the physiopathologic mechanism of angina pectoris is an insufficiency of the coronary arterial blood flow. This is true for all degrees of angina: simple angina (due to acute transient coronary insufficiency), major angina (due to acute coronary occlusion and myocardial infarction), and the subacute, intermediate conditions (indifferently called "coronary failure" or "coronary insufficiency"). Thus, the common denominator of these clinical entities, apparently very different, is the disproportion between the needs of the heart for oxygen and the inadequate supply of blood.

There are many anatomic causes of angina pectoris, coronary atherosclerosis being by far the most common. The less common causes of angina pectoris

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Received for publication March 30, 1959.

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are (1) aortic valvular disease: aortic valvular stenosis and aortic insufficiency, (2) syphilitic aortitis, the responsible factors being either the coronary ostial occlusion alone or the combined ostial occlusion and aortic insufficiency, (3) severe anemia, (4) thyrotoxicosis, with increased demands by the heart for oxygen, and (5) the hypothetical coronary artery spasm which would cause a sudden and sometimes prolonged decrease in the supply of blood to the heart. Anemia and thyrotoxicosis alone, however, are rarely capable of producing a myocardial hypoxia sufficient to induce anginal pain, but they are certainly aggravating factors when some other cause of coronary insufficiency is already present.

Actually, the problem of angina pectoris can be summarized under one main etiologic disease—coronary atherosclerotic stenosis. "Coronary artery disease," "coronary artery heart disease," and, more recently, "ischemic heart disease" (World Health Organization, Geneva, 1955) are among the various appellations which have been offered for this condition.

In this paper we will deliberately disregard the uncommon causes of coronary insufficiency, and be concerned only with the management of angina pectoris due to ischemic heart disease. Moreover, following the traditional ideas, the treatment of acute coronary occlusion will be excluded from this study.

MANAGEMENT OF ANGINA PECTORIS DUE TO ISCHEMIC HEART DISEASE

First of all, the treatment of the anginal attack itself must be distinguished from the prophylactic treatment of the anginal attacks. Indeed, although one magic drug and a few subsidiary procedures effective in relieving the anginal paroxysm are available, we are still unable to prevent the recurrence of these paroxysms, that is, to control the cause itself of the symptom angina. This accounts for the efflorescence of numerous chemical, physical, psychiatric, and surgical methods which have been proposed for the prophylaxis of angina. In the field of medicine, the profusion of therapeutic procedures is an unmistakable sign of the physician's helplessness when confronted with the disease.

I. TREATMENT OF THE ANGINAL ATTACK

The use of *glyceryl trinitrate* (nitroglycerin; trinitrine in France), introduced by Murrell[30] in 1879, represents the entire treatment of the anginal attack. In France, nitroglycerin is available in sugar-coated tablets containing 0.5 mg. of nitroglycerin in a 1/100 alcoholic solution. The patient chews the tablet, and the solution is absorbed by the buccal mucosa. Some pharmaceutical preparations contain nitroglycerin in combination with one or several other drugs such as caffeine, papaverine, scilla, scopolamine. These combinations do not add to the efficacy of the tablets but they provide a variety of prescriptions that may be useful. We have often compared the effects, in the same patient, of the 0.3-mg. sublingual tablet of nitroglycerin and the 1/100 trinitrine-solution tablet. The former seems to have more prolonged action and its use is more agreeable to the patient. However, in a minority of cases the trinitrine tablet was superior. Patients are advised to take nitroglycerin at the onset of the attack, without waiting for its full development. If one tablet provides only partial relief, a

second one can be taken a few minutes later. The patient is instructed to call his physician if the attack does not respond to three or four tablets, because this sustained pain may be due to a sudden aggravation of the coronary insufficiency.

Nitroglycerin can also be usefully employed prophylactically. Often the patient knows by experience the circumstances which produce pain, and the prophylactic use of nitroglycerin will spare him not only the physical discomfort and the danger but also the vexation and mental depression associated with anginal pain.

Sometimes the indications and dangers of nitroglycerin are misunderstood not only by the patient but by his family physician. They fear the occurrence of a refractory state to the drug. Such a refractory state is exceptional and we have never observed it. Those of our patients who no longer responded to nitroglycerin were actually in an evolutive phase of ischemic heart disease, and the persistent pain was the reflection of the increasing cardiac hypoxia. The side actions of nitroglycerin, such as headaches and congestion of the face, are rarely of such intensity as to necessitate suspension of the medication. Sudden syncopes are exceptional. The possible occurrence of methemoglobinemia can be overlooked because of its extreme unlikeliness.

The beneficial effect of nitroglycerin on the anginal attack is quasi-constant and strikingly rapid. Used prophylactically, it enables the patient to have a fairly normal activity for 15 minutes to 1 hour. It remains the most dramatically effective therapy for attacks of angina pectoris, as demonstrated by 80 years of clinical experience.

Nevertheless, the mechanism of action of nitroglycerin remains unsettled. As a rule, it is agreed that nitrites relieve angina pectoris by producing a prompt, but transient, coronary vasodilatation, thus stopping the acute myocardial ischemia and allowing, during a brief lapse of time, an adequate adjustment of the supply of oxygen to the needs of the heart. This "mechanistic" explanation has been questioned. Raab and Lepeschkin[34] think that nitroglycerin might interfere with the "epinephrin sympathin" induced chemical anoxia of the myocardium that would be the substratum of the symptom angina. Besides its mechanical action (vasodilatation), which they do not deny, nitroglycerin would also, and chiefly, have an antiadrenergic, hence, a metabolic, action on the anoxic heart. This interesting concept might account for the contradictions that have been reported in certain experimental observations—such as the absence of increase in coronary blood flow after administration of nitroglycerin.

As to the paradoxical effects of nitrites demonstrated by certain investigators[11,38]—"coronary-like" alterations in the electrocardiogram of coronary patients after oral administration of nitroglycerin or inhalation of amyl nitrite—they may be understood on the basis of an excessive pooling of blood in the peripheral veins, with a resultant decrease of the cardiac filling and, consequently, of the coronary flow. This is, however, too uncommon to have any practical import.

Amyl nitrite is used by inhalation to relieve the attack of angina. Its action is immediate, sometimes excessive, and of rather short duration. As a rule, patients prefer the nitroglycerin tablets.

Besides the nitrites, *stimulation of the carotid sinus reflex*,[26] a method first mentioned by Wassermann[41] in 1928, is a procedure that may be strikingly effective on the anginal pain. A firm massage is performed on the region of one carotid sinus, and if there is no response, the same procedure is repeated on the opposite side. Pressure should never be exerted on both sides simultaneously because of the real danger of cerebral accidents. We have often observed the prompt and reliable effectiveness of such stimulation, sometimes after trinitrine had failed. In opposition to Freedberg and Riseman,[15] we do not believe that its action is fugacious. As a rule, an attack of angina which has responded to this procedure does not recur in the following minutes, even in patients who usually experience prolonged attacks. The mechanism of action of the carotid sinus reflex on angina pectoris is still disputed. There is no definite evidence that this reflex produces a coronary vasodilatation. It possibly induces simultaneously a vagal excitation and a sympathetic inhibition. The hypothesis of a direct stimulation of the cerebral center remains to be proved. Nevertheless, it is interesting to point out the apparent paradox of using the carotid sinus reflex as a treatment of anginal attacks if one keeps in mind the general belief that vagal stimulation produces coronary vasoconstriction. The dangers of carotid sinus stimulation should not be overlooked: syncope, convulsions, hemiplegia, or other neurological disturbances, and sudden death may occur. For this reason the procedure should be performed solely by the physician, and patients should be instructed not to apply it themselves. Moreover, this measure is contraindicated in elderly patients in whom a hypersensitive carotid sinus is combined with a presumably poor cerebral vascular system.

Alcohol was, before the nitrites, the medication used for the attacks of angina pectoris. The beneficial effects of brandy and whisky on cardiac pain were emphasized by early authors. It is questionable[37] whether alcohol, according to the classic opinion, produces a rapid coronary vasodilatation. It is more likely that its action is dependent on its sedative and analgesic properties (elevation of the threshold of perception of cardiac pain) combined with its euphoric virtues. The value of alcohol in the attack of angina pectoris has greatly decreased since the introduction of nitroglycerin; however, a moderate quantity of alcohol may in certain circumstances prove helpful as an additional prophylactic medication.

II. PROPHYLACTIC TREATMENT OF ANGINA PECTORIS

The numerous prophylactic treatments of angina pectoris due to ischemic heart disease are based upon six rational principles: (1) to treat the anatomic cause itself, namely, atherosclerosis, by retarding its progress and, if possible, by reducing the existing lesions; (2) to increase the coronary blood flow; (3) to diminish the metabolic needs of the heart; (4) to inhibit transmission of the cardiac pain; (5) to eliminate, or at least diminish, the contributing factors of myocardial hypoxia; and (6) to act upon the upper nervous centers in order to elevate the threshold of perception of cardiac pain.

A. *Treatment of the Anatomic Cause of Atherosclerosis.*—The solution of the basic problem of anatomic cause of atherosclerosis would be the clue to the prophylactic treatment of angina pectoris. It still remains to be found. We know but little about the genetic factors which are certainly of primary importance, and we are as yet unable to influence them. The ethnic and geographic aspects of atheroma, and the social, mental, and professional factors have given rise to many speculative discussions which have yielded no definite conclusions. Much has been proposed and but little proved concerning the emotional factors and the way of living which would contribute to produce and/or to precipitate arterial degeneration. Indeed, who can affirm that the twentieth-century man is submitted to stronger emotional stress than the slave of antiquity, the serf of the Middle Ages, the agnostic of the Inquisition, or even the simple man of the Dark Ages.

It is thought that dietetic factors contribute to a great extent to the genesis of atheromata. Without venturing into the jungle of biochemical dialectics, we may, however, ask some questions. Does the arterial atheromatous degeneration result from an impaired metabolism? Is this impairment related to a simple total caloric imbalance in favor of the intake (obesity)? Or is it related more specifically to a disturbance of lipid metabolism? Does this disturbance of lipid metabolism result from an excess of saturated fatty acids (lipoprotein macromolecules)? Does the increased level of serum cholesterol play a definite part in the genesis of the coronary degenerative lesions? The answers to these questions are as yet uncertain.

An unwieldy literature has been discussing, especially during these last 10 years, the atherogenic properties of certain fats, the innocuousness of others, and even the beneficial action of a third category. Faced with numerous affirmations, refutations, and contradictions, all based upon apparently reliable chemical studies, the clinician remains uncertain. From a practical viewpoint it is important to know whether a drastic reduction of the dietary intake of saturated fatty acids is justified in coronary patients, regardless of the serum cholesterol level, and whether the unsaturated fatty acids, represented by vegetable oils, such as olive, peanut, or more specifically, Indian corn oil and safflower oil, are useful adjuncts to the diet.

Various medications have been proposed to lower the level of cholesterolemia or, more precisely, to correct the impaired lipoprotein metabolism. Almost all these drugs have sunk into legitimate oblivion. Some of them, however, are worth mentioning. The use of heparin as a "clearing factor" acting on the lipoprotein macromolecules was proposed in 1951, as an etiologic treatment of atherosclerosis.[17] Fifty to 100 mg. are administered intravenously once or twice a week, or 200 mg. of long-acting heparin are administered intramuscularly or subcutaneously once a week, indefinitely. Our experience, based upon 4 years of systematic use of this treatment in our coronary patients, has not convinced us of its value. Other authors[32] had already expressed their disappointment in 1953.

Estrogens have been proposed on the basis of experimental studies, inhibition of the cholesterol-induced atherosclerotic process in the chick and depression of

the plasma total cholesterolphospholipid ratio in postmenopausal women.[31] We have used estrogens in a few of our male coronary patients, without conclusive results. Each time, we were obliged to discontinue the therapy because of disturbing side effects (digestive disorders, feminization, swelling of the breasts, decrease of sexual potentia). In only one of our patients, who was treated daily with estrogens for a prostatic carcinoma, did we observe a consistent and durable alleviation of angina pectoris. Conversely, in another patient who received massive doses of estrogens for the same reason, angina increased in spite (or because ?) of the estrogens, and an acute myocardial infarction occurred during the treatment.

Nicotinic acid administered in high doses (1.5 to 3 Gm. daily) was reported to have an anticholesterolic action.[1] We have no experience with this drug.

Sitosterol was proposed for the same reasons, and the question has been raised as to whether the anticholesterolic action of the "therapeutic" vegetable oils (corn, safflower) is due to the presence of sitosterol in their molecule.

Chelators have been proposed for the treatment of angina pectoris.[9a] Further studies are required to evaluate their action. However, it is doubtful whether subtraction by chelation of the calcium which infiltrates inconstantly into the atherosclerotic coronaries would have an action on the atherosclerotic degenerative process itself.

B. *Treatment of Angina Pectoris Based Upon the Increase of Coronary Blood Flow.*—The concept that angina pectoris results from a reduction of the coronary vascular bed by the atherosclerotic process, possibly combined with an aggravating factor of vasoconstriction, has led quite naturally to attempts to produce a diffuse coronary vasodilatation capable, presumably, of increasing the coronary flow and thus of correcting myocardial hypoxia. Most of the medical methods are designed to produce a sustained coronary vasodilatation and are used on the basis of experimental observations dealing, as a rule, with normal animals. Unfortunately, many variables interfere with the regulation of cardiac irrigation. "The coronary blood flow varies with the heart rate, the aortic blood pressure, the caliber and resistance of the coronary arteries, the coronary venous pressure, the blood viscosity and the phase and strength of ventricular contraction. All of these in turn are dependent on factors such as the nervous control of the coronary arteries, metabolic changes in the heart muscle, intra-auricular and intraventricular pressures and the degree of cardiac dilatation."[8] Furthermore, the doses administered in experimentation exceed, often to a great extent, the therapeutic doses. Also, the same drug may have quite a different action on different kinds of animals. These facts partly account for the surprisingly contradictory opinions concerning the effectiveness on angina pectoris of almost all the drugs which have been endowed with vasotrophic properties. Doubt and confusion are still increased, on the one hand, by the remaining uncertainty concerning the action of the vagal and sympathetic nerves on coronary vasotrophicity, and, on the other hand, by the extreme difficulty encountered in evaluating the clinical results of a drug.

In many works the results are judged on the basis of the study of electrocardiographic tests following exercise (two-step test, etc.). We agree with other

authors[10] that this method, in spite of an apparently scientific precision, is not reliable, for the fundamental reason that angina pectoris is by essence a "symptom-complex," the painful *subjective* manifestation of myocardial hypoxia. It cannot be evaluated according to the occurrence, disappearance, or fluctuations of electrocardiographic changes that explore an *objective* parameter. Besides, if one takes into consideration the great variety of factors capable of producing "coronary-like" alterations of ventricular repolarization, one can appreciate the uncertainty of a judgment based solely or chiefly on this criterion. The increasing place occupied in the field of electrocardiography by the metabolic or neurometabolic disturbances of the myocardium justify all the more this wariness. Consequently, we think that the effectiveness of an antianginal, supposedly vasodilating drug cannot be judged on the sole basis of the results of electrocardiographic tests. Improvement of angina pectoris must be judged by the disappearance or consistent decrease in intensity, frequency, and duration of the anginal attacks.

But here new difficulties arise. First, there is the involuntary partiality of the observer, who has a natural tendency to interpret facts according to his desires, his hopes, or his scepticisms. This serious objection could be avoided by the routine use of the "double-blind" method proposed by Greiner and associates[18] in 1950. The objectivity assured by this method is much superior to that of the simple "placebo method,"[16] at the cost, it is true, of many practical difficulties. Up to now most of the reports concerning the assay of antianginal medication are not based upon the double-blind method.

Another difficulty encountered in the evaluation of a drug on the basis of subjective data alone—the walking-tolerance, for instance—arises from the more or less unconscious partiality of the patient himself. His wish to cooperate or, conversely, his hostility toward the new medications has a great influence on his verbal response. A great deal of patience, diplomacy, and experience are required to distinguish the truth.

Lastly and chiefly, the main difficulty is due to the spontaneous and quite unexpected variations of angina pectoris in a given patient. A patient may suffer ten attacks of angina daily for weeks or months, and then suddenly, without treatment, walk easily and painlessly; another may experience a sudden aggravation of his symptoms without apparent reason; and in other patients the course of angina pectoris varies capriciously from one day to another. The existence of these variations, as yet baffling to the physician, should be kept in mind so as to avoid rash interpretations of therapeutic results.

Yet, in spite of these undeniable causes of error, we feel that the effectiveness of an antianginal therapy should be basically evaluated by the history of the patient. If he uses less nitroglycerin, and if he can perform painlessly those activities which used to, under the same circumstances, provoke an attack of angina, then it can be said that the drug is undoubtedly effective, even if the electrocardiographic alterations are still present. At least, the symptoms of ischemic heart disease are less severe, even if chronic hypoxic myocardial deterioration is latently following its course. The mental relief which results from

the alleviation of angina pectoris is not to be underestimated, even though sudden death may unexpectedly occur, thus demonstrating that the disappearance of angina does not necessarily imply cure of the coronary disease.

Attempts to increase the coronary blood flow are based upon two methods: medical and surgical. Medical methods deal with drugs that are presumably coronary vasodilators. Among the great variety of medications available, two different groups are the most widely employed, the nitrites and the xanthines.

The long-acting nitrites: The dramatic effectiveness of nitroglycerin on the attack of angina has led to the search for other nitrite compounds the action of which would be as powerful and much more sustained. These drugs are designed to protect the coronary patient all through the day. Sodium nitrite is of little interest. Pentaerythritol tetranitrate (Peritrate) and triethanolamine trinitrate (Metamine) are at present widely employed. Peritrate is administered orally in doses of 10 to 20 mg., two to four times a day, and Metamine is given orally in doses of 2 mg., three or four times a day. These drugs are also available in "sustained-action" tablets which are supposed to be active over a period of 10 to 12 hours. More recently, sustained-action tablets of nitroglycerin containing 2.4 to 6.0 mg., and given orally instead of sublingually, have been marketed (Nitroglyn). Even in low dosage, however, the long-acting nitrites may have unpleasant side effects (headaches, nausea, vomiting).

A recent comparative study of the respective value of different nitrite preparations has demonstrated that the route of administration represents the main factor of their effectiveness.[35] The sublingual administration is the most effective because nitrites are partly inactivated in the gastrointestinal tract. Unfortunately, all the nitrites cannot be administered sublingually.

Favorable claims have been made for the effectiveness of a nitroglycerin ointment.[13] A 2 per cent ointment is applied once or twice a day on the anterior thoracic region. This preparation would have a consistent and sustained action (5 to 6 hours). We have no personal experience of this method.

The xanthines: The most commonly used are theophylline and aminophylline (theophylline ethylenediamine). They can be administered by four different routes: oral, rectal, intravenous, or intramuscular. Numerous commercial preparations are available which differ only in slight chemical variations or in the addition of various sedatives. Choline theophyllinate is a new preparation recommended by Aravanis.[3] Theophylline, choline theophyllinate, and aminophylline are given orally in tablets of 100 to 150 mg., one to three tablets, two or three times daily. Higher doses frequently produce gastric distress, headaches, or insomnia. Suppositories are usefully prescribed because they allow the use of higher doses, 350 to 500 mg., thus approaching the dosage which experimentally produces coronary vasodilatation in animals. Intravenous or intramuscular administration secures a rapid absorption of high doses, 250 to 500 mg. in each ampule.

Besides the long-acting nitrites and the xanthine compounds which are widely prescribed in coronary patients, various other drugs, supposedly coronary vasodilators, are in use. *Atropine* and *histamine* are of little interest. The action of the *ganglion-blockers* on angina pectoris has not been demonstrated and these

drugs may have dangerous side effects (sudden systemic hypotension, intestinal paresis). *Alpha-tocopherol* can be disregarded. The use of the *cinchona alkaloids* in the treatment of angina pectoris was introduced in 1795,[5] but it is only in the last 15 years that these compounds have been studied consistently. The effectiveness of the cinchona alkaloids, especially quinidine and quinine, appeared to be demonstrated in 1954, by the work of Riseman and his associates.[36] This action was related to the quinoline ring. Actually, our personal experience has not been conclusive. We have often prescribed quinidine in our coronary patients over long periods of time in order to control cardiac arrhythmias, without noticeable alleviation of angina pectoris.

Iodine is, at least in Europe, a classic medication of angina pectoris—no doubt because it is a routine medication in gerontology. Its use is based upon the ancient belief in the antiatheromatous and vasodilator virtues of the iodides. After having largely prescribed this drug during 10 years, we have now given up its use for want of any conclusive results in our patients, except in authentic cases of myxedema apparently induced by the intramuscular administration of an iodine preparation. We felt that this involuntary therapeutic myxedema accounted for the subsequent improvement of angina pectoris. These cases are, however, too rare and unpredictable to justify the systematic use of this method in coronary patients.

Rauwolfia serpentina and its principal alkaloid, *reserpine*, used, as a rule, for their hypotensive and sedative action in hypertensive patients, have also been claimed to have a prophylactic action on angina pectoris. In any case, they can be safely prescribed in hypertensive coronary patients, whereas the use of other hypotensive drugs such as hydralazine and the various ganglion-blockers has seemed to us undesirable.

Papaverine, opium alkaloid of low toxicity without narcotic effect, is a classic medication of angina pectoris because of its coronary vasodilator properties, which have been demonstrated experimentally. High doses are required, 180 to 300 mg. daily. Synthetic papaverine compounds are available, such as dioxyline (Paveril) administered in doses of 200 mg., three or four times daily. These drugs may be somewhat useful in angina pectoris.

Khellin, which is extracted from the seeds of an Egyptian plant, *Ammi visnaga*, has given rise to great hopes and enthusiastic reports since it was first studied in 1946, by Anrep and associates,[2] who reported 56 per cent successful results. Experimentally, khellin has powerful coronary vasodilator properties. Unfortunately, the effective doses readily produce digestive disturbances (gastralgia, nausea, vomiting) and headaches. The doses used clinically, 40 to 80 mg. daily, are well tolerated but have no definite action on angina. To avoid the digestive side effects, khellin can be administered intramuscularly in doses of 50 mg., every 12 to 24 hours. Khellin may sometimes be a helpful medication but its action is very inconstant and its use limited by undesirable side effects.

Methyl-3-chromone has been assayed in France (Diacromone) with successful results.[40] It is administered orally in tablets of 100 mg., three or four times daily. Its side effects are insomnia and excitation. Our personal experience has not convinced us of the value of this drug.

Most of the drugs mentioned above are combined, in pharmaceutical products, with analgesic, sedative, or "tranquilizing" agents such as phenobarbital, aspirin, meprobamate, rauwolfia, in various proportions. Thus, when a favorable result is observed, it is difficult to distinguish what is due to the presumably vasodilating agent and what to the sedative or analgesic agent. The uncertainty in regard to the effectiveness of the purely vasotrophic drugs accounts, no doubt, for the wide use of these preparations.

The action of the tissue extracts from the heart, the liver, the pancreas, the placenta has not been demonstrated.

In Europe, where the ancestral myth of the mysterious virtue of thermal baths is deep-rooted in the patients as well as the physicians, the anginal patients are often advised to spend 3 weeks a year at Royat, Bain-les-bains, or Bad-Neuheim, with the naive hope of increasing the coronary reserve for one year with the carbonated-gaseous waters. We have not been convinced of the effectiveness of these thermal seasons which are deprived of all rational basis, and are, furthermore, often tiring and always costly.

After having prescribed the above-mentioned drugs to thousands of coronary patients, our inmost conviction is that not one of them has a general therapeutic value, definite and constant—whatever may be the experimental basis of its use. Each of these drugs has had enthusiastic supporters and vehement detractors, all of whom may have been right. Actually, each patient represents a special case, and a prophylactic medication, elsewhere ineffective, may have an authentic action on an occasional patient, for reasons as yet unknown. A similar opinion has been expressed by Kory and associates.[24]

Surgical attempts to increase the coronary blood flow can be divided into the following three groups: (1) Those which have the objective of increasing the coronary collateral circulation by extracardiac communications, which can be achieved by various procedures: implantation of various vascular structures (pectoral muscle, omentum, left lung) in the myocardium; implantation of the left internal mammary artery into the wall of the left ventricle (Vineberg); ligation of both internal mammary arteries (simple and anodyne procedure performed under local anesthesia)[29]; and abrasion of the visceral pericardium, or pericardial irritation with various agents, talcum, bone meal, or asbestos (Beck I). (2) Those which have the objective of improving the distribution of oxygenated blood by ligation or stenosis of the coronary sinus, arterialization of the coronary sinus, mechanical or chemical de-epicardialization, or pericoronary neurectomy. (3) Those which have the audacious objective of removing the coronary stenosis by endarterectomy or by replacement with a vascular graft.

An excellent critical study of these procedures has been published recently by Hellerstein.[21] We agree with his conclusions that "myocardial revascularization" surgery is still at present in its experimental stage and is advisable only in those cases of intractable angina pectoris which we will discuss later. Because of the high mortality of most of these procedures, and their unpredictable results, the surgical methods of myocardial revascularization must still be considered as a "heroic" treatment of angina pectoris.

C. *Treatment of Angina Pectoris Based Upon the Reduction of the Metabolic*

Needs of the Heart.—Reduction of the metabolic needs of the heart is reached by the creation of therapeutic myxedema, which reduces the basal metabolism and thus the need of the heart for oxygen. At first,[7] myxedema was produced by throidectomy. Later, the thiourea derivatives were used, with questionable results. At the present time, inhibition of the hormonal secretion is induced by radioactive iodine (I^{131}), according to the method proposed by Blumgart and his associates.[6] These authors reject the use of a single dose because of the dangers of acute thyroiditis, with sudden increase of the basal metabolism. The total dose of radioactive isotope, which depends on the I^{131} thyroid uptake, is given in three divided doses at weekly intervals of 10 or 20 millicuries each. This method has been modified recently by Segal and associates,[39] who give lower doses at intervals of 2 or 3 months. The signs of hypothyroidism appear between the eighth and twelfth weeks. The disappearance or reduction of the anginal attacks should be concomitant. Later, very small doses of thyroid extracts (5 to 30 mg. daily) may be given, with the objective of achieving an adequate balance between tolerable hypothyroidism and still improved angina pectoris.

Seventy-five per cent good results were observed in anginal patients treated with radioactive iodine. The relief of angina pectoris may not be due solely to the reduction of myocardial metabolism, but also to other factors which may interfere,[6] such as decrease of the sensibility of the cardiovascular system to adrenergic mediators, changes in the perception of pain, increased rate of development of intercoronary anastomosis.

The risk and disadvantage of this method are to create a new disease, myxedema, in order to abolish or diminish the symptomatic expression of another disease, without being able to cure the latter. Indeed, there is no evidence that life expectancy is increased by therapeutic myxedema, which probably has no beneficial action on the arterial degenerative process. The patients must be made duly aware of the unpleasant effects of the method—intellectual and physical sluggishness, decrease or disappearance of sexual potentia, frigidity, morphologic alterations. In conclusion, we think that the creation of myxedema by radioactive iodine should be regarded, just as the surgical procedures, as a "heroic" method of treatment advisable only in intractable cases of angina pectoris.

D. *Treatment of Angina Pectoris Based Upon the Interruption of the Painful Impulses From the Heart.*—It is usually agreed that the anginal pain arises in the intramyocardial sympathetic fibers which are in contact with the ischemic cardiac cells. The stimulus is either hypoxia itself or a compound, as yet unknown, resulting from the inadequate elimination of metabolic products. The suggestion of relieving angina pectoris by sympathectomy was made as early as 1899.[14] This was realized for the first time in 1916.[22] Since then numerous procedures dealing with the sensory pathways of cardiac pain have been proposed to eliminate the symptom angina. Some authors have even claimed to have increased coronary blood flow by temporary or definitive sympathetic inhibition. This has not been demonstrated. Some methods, such as the Novocain infiltrations of the stellate ganglia[25] or of the preaortic plexus,[4] have only a temporary action. However, the repetition of these procedures may produce a durable disappearance of angina.

The object of the surgical methods is to realize an authentic and definitive sensory "denervation" of the heart. Briefly, five different procedures can be distinguished: (1) paravertebral injection of ethyl alcohol into the upper thoracic (T_1 to T_4) sympathetic ganglia, (2) resection of the upper thoracic (T_1 to T_4) sympathetic ganglia, (3) bilateral section of posterior sensory spinal roots (upper four thoracic spinal roots), (4) unilateral stellate gangliectomy, and (5) resection of the preaortic plexus.

It was objected that these procedures, by abolishing anginal pain, suppressed a useful warning to the patient. It is now known, however, that after neurectomy the pain of angina pectoris is replaced by a dull sensation which makes the patient aware that his heart is suffering and that he must rest. The actual objections to these surgical measures are (1) that they do not correct the physiopathologic mechanism—coronary insufficiency—of angina pectoris, (2) that the mortality risk of the most radical procedures is too high, and severe postoperative complications are possible (intolerable intercostal neuralgia), and (3) that they often fail to give any results, or the results are inconsistent or only temporary. Angina often recurs a few months after neurectomy, the temporary relief being possibly purely psychogenic in origin. Regeneration of the sympathetic fibers may account for the later recurrences of angina pectoris.

For all these reasons we think that the different methods of cardiac denervation are only indicated as a last recourse, in a minority of cases.

E. *Treatment of Angina Pectoris Based Upon the Elimination of the Contributing Factors.*—It is well known that many pathologic conditions unrelated to ischemic heart disease contribute to the production of attacks of angina. The most common are (1) osteoarticular lesions (cervicodorsal spine, shoulder, sternochondral and chondrocostal articulations), (2) digestive disorders (cholelithiasis, peptic ulcer, gastritis, diaphragmatic hernia), (3) bronchopulmonary disease (asthma, bronchitis, pulmonary emphysema), (4) cardiac arrhythmias (premature beats and especially paroxysmal tachycardia), (5) systemic arterial hypertension, which is so often associated with ischemic heart disease, (6) primary or secondary anemia which contributes to increase cellular hypoxia (at the same time that it stimulates the development of functional intercoronary anastomosis), and (7) hyperthyroidism. If possible, these contributing factors should be corrected, for in many instances they make apparent an otherwise asymptomatic coronary insufficiency. If surgical correction is judged necessary, it must be kept in mind that the mortality risk in coronary patients is about three times the standard risk. Thus, only unavoidable surgery is justified in these patients.

In treating the associated diseases in a coronary patient, the physician should not confuse the aggravating factor with the etiologic factor. The etiology of angina pectoris is coronary insufficiency and not, for instance, cholelithiasis or spinal osteoarthritis. Thus, to avoid cruel disappointments, the physician should not promise, nor expect, too much from the treatment of a contributing factor.

F. *Treatment of Angina Pectoris Based Upon the Elevation of the Threshold of Cardiac Pain.*—Elevation of the threshold of cardiac pain is the object of the use of sedative, analgesic, and tranquilizing agents. Furthermore, these drugs

may have, thanks to their sedative action on the central nervous system, beneficial effects on the coronary blood flow. The drugs most widely used are: (1) the malonylurea derivatives, especially phenobarbital, 50 to 150 mg. daily, (2) acetylsalicylic acid, 0.50 to 2.50 Gm. daily, (3) rauwolfia serpentina, 300 mg. daily, or its derivatives, (4) meprobamate, 1.2 Gm. daily (which can be usefully associated with reserpine 0.1 mg.), (5) hydroxyzine (Atarax), 30 to 75 mg. daily, (6) chlorpromazine, 25 to 50 mg. daily (the multifold properties of this neuroplegic agent still require further investigation), and (7) promethazine (Phenergan), antihistaminic and sedative drug with strong soporific properties which can be prescribed in the evening, one tablet of 25 mg. or 5 to 15 c.c. of syrup containing 1 mg. per cubic centimeter.

Recently, the antianginal properties of isoproniazid (Marsilid), isopropilic derivative of isoniazid, have been fortuitously discovered.[9] The neurologic effects of this drug are used in psychiatry. Its mechanism of action on angina pectoris is unknown; it may be related to its cerebral action or partially to enzymatic changes in the myocardial tissue (?). The suggested daily dose of 100 to 150 mg. may produce disturbing side effects (giddiness, weakness, faintness, genitourinary disturbances, syncope). Lower doses (20 to 50 mg. daily) have seemed to us more adequate. To avoid habituation this drug must be discontinued from time to time. In spite of recent enthusiastic reports[12,27] our first results have not yet convinced us that Marsilid is "a specific drug for the treatment of angina pectoris."[9]

All the above-mentioned drugs can be used in various combinations. They readily potentiate one another, hence the necessity of starting with small doses.

The effects of these sedative agents on the perception of pain and on the emotional tension and anxiety of the coronary patients are undoubtedly beneficial. The adequate adjustment of an individual treatment for each patient depends upon the skill and wisdom of the physician. The object of sedative therapy is to provide the patient with peace and comfort without depressing his faculties to the point of disabling him in the performance of his daily activities.

The place of opiates in the treatment of angina pectoris is well defined. As a rule, these drugs are not indicated in coronary patients, except in the cases of myocardial infarction, because of the risk of addiction. However, in the instances of *evolutive* subacute coronary insufficiency, characterized by the repetition of severe and prolonged attacks, the use of opium and its derivatives is justified. A subcutaneous injection of 10 mg. of morphine hydrochlorate, one to three times a day, may be required, but this treatment must be discontinued as soon as possible. This method has always rewarded us with gratifying results, and patients who had been tormented by frequent anginal attacks and by the dread of their recurrence, recover sleep, peace, and euphoria. On the contrary, in cases of "intractable" angina pectoris the opiates are contraindicated because of the obvious dangers of addiction.

Recently, a new analgesic compound has been proposed, Pyrrolamidol (R. 875 or Palfium in France), available in tablets of 5 mg. Its indications are similar to those of the narcotics. This drug has not yet been extensively studied.

The use of therapeutic narcosis and of hypnotic suggestion would perhaps

be helpful in some circumstances. To our knowledge these methods have not been systematically applied as a treatment of refractory cases of angina pectoris.

THERAPEUTIC APPROACH TO TREATMENT OF ANGINA PECTORIS

After having discussed the different prophylactic methods of treatment of angina pectoris, we will now be concerned with the rules which may guide the physician in his approach to each individual case. The choice of a method depends essentially on the evolutive phase of the disease. We think that the distinction between an acute and a chronic phase of ischemic heart disease is based upon sound clinical evidence.[33] According to this concept three different situations may be defined, each requiring a different therapeutic approach: (1) chronic angina pectoris, (2) subacute evolutive angina pectoris, and (3) intractable angina pectoris. Of course, coronary artery heart disease does not necessarily pass through these three phases.

Chronic Angina Pectoris.—Chronic angina pectoris is the expression of an "inactive" phase of ischemic heart disease. To this category belong the patients who have been suffering for months or years with attacks of angina always produced by the same circumstances, exertion and/or emotion. The pain subsides spontaneously after a few minutes or is instantaneously relieved by nitroglycerin. The level of the diminished coronary reserve is fixed, and pain occurs only when it is exceeded. In these cases the "heroic" treatments, surgery and induced myxedema, must be discarded, and likewise, permanent anticoagulant therapy is not indicated. Contributing factors should be eliminated insofar as possible. The patient should be instructed to submit himself to a few basic rules drawn essentially from simple common sense. A moderately low caloric diet is advisable and heavy rich meals should be avoided. Obese patients should lose weight, because obesity is known to be an aggravating factor in a poorly irrigated heart.[28] Qualitatively, alimentation should be varied and palatable. Vegetable fats (corn, safflower oil) should be substituted for animal fats (saturated fatty acids). Patients, however, should not be encouraged to live under the ridiculous obsession of their cholesterol level, all the more so since the determination of plasma cholesterol is often highly illusory in current practice.

The harmful effect of tobacco on coronary patients has not been established except in a few patients who experience cardiovascular reactions after smoking 2 or 3 cigarettes. We have been impressed, however, by the fact that the great majority of our middle-aged coronary patients are heavy smokers (20 to 60 cigarettes daily), and we usually advise them to stop or to reduce the use of tobacco. An exception must be made for the individuals in whom suppression of tobacco induces nervous disturbances, no doubt more harmful to the heart than nicotine itself. It must also be mentioned that the suppression of tobacco is often followed by an increase in appetite and, thus, an undesirable gain of weight.

Moderate quantities of coffee and tea can be taken, except in the evening when they might interfere with sleep. Likewise, a few alcoholic drinks are permitted.

The regulation of the way of living depends on the limits of the coronary reserve, that is, all those activities are permitted which can be performed without pain. Very often patients suffering from chronic angina pectoris can keep a full-time job. Physical exercise is allowed, and even advised, if one assumes that exercise is one of the best factors in the development of intercoronary anastomoses. Thus, walks at a slow pace and golf are permitted; hunting and fishing are sometimes also possible. Entertainment, such as shows and social activities, is desirable as long as it is not associated with too much mental or physical excitement. Sexual intercourse is permitted, provided it is easy, not too prolonged, and not too frequent. The prophylactic use of a tablet of nitroglycerin may often help a patient to accomplish sexual intercourse without the underlying dread of an anginal attack or of sudden death. Trips, for business or pleasure, are allowed if accomplished at leisure. For very long trips the use of pressurized airplanes is advisable. Vacations should be as long and as frequent as possible. Thermal waters are undesirable. Altitudes higher than 1,000 to 1,500 meters, and cold and windy seasides are, as a rule, to be avoided. Most patients do not tolerate cold or very hot and humid climates. A warm, temperate, and dry climate is the most favorable. Actually, each individual should spend his holidays where he feels best.

The precautions concerning surgical operations are well known. Since the mortality risk is three times higher than the standard levels, only unavoidable operations are justified.

Last but not least, it is of great importance that the patient adopt a peaceful and optimistic attitude toward his chronic disease. It is part of the physician's role to help him achieve this attitude. Because the term "angina pectoris" is associated with the risk of sudden death, it is a custom to conceal from the patient the real nature of his symptom. The words "false angina," "nervous spasms," "aerophagia," or "aortitis" are commonly used. Although this medical attitude is based upon generous feelings toward the patient, we do not believe that it is profitable. We think it is better to explain to the patient the significance of his symptom, namely, that it reflects an inadequate circulation of his heart because of damaged blood vessels. As often as possible the term "angina pectoris" should be openly used and striped of its "taboo" character. However, this attitude must not be adopted with anxious, neurotic individuals or with individuals of low intellectual level. Once the mechanism of his complaint has been explained to the patient, the really encouraging aspects of his disease must be optimistically presented— the chance of a prolonged life span, the ability to lead an active and useful life, the possibility of an anatomic improvement with disappearance of the symptoms because of the development of intercoronary anastomoses. Thus, the patient is aware of the different aspects of his disease and of what he may expect in the future, and he will accept more cheerfully a newly regulated life.

Drug therapy could be limited to the adequate use of nitroglycerin. However, although there is no specific prophylactic treatment of angina pectoris, a usually ineffective drug may improve an occasional patient, and in any case the physician is obliged, nine times out of ten, to prescribe medications to satisfy

his patient. We advise the use of a long-acting nitrite combined with a sedative or tranquilizing agent (phenobarbital, meprobamate, or reserpine). Aminophylline or theophylline and papaverine may also be given in association. We sometimes prescribe, without great conviction, a weekly injection of heparin over long periods. We have, however, observed no significant difference between the large group of drug lovers and the small group of wise men who are content to regulate their way of living according to a few rules and to take nitroglycerin when necessary.

Evolutive Angina Pectoris.—Evolutive angina pectoris represents an active phase of ischemic heart disease. To this category belong two groups of patients: those who are seen at the onset of their disease characterized by attacks of angina on exertion and/or at rest; and those who have been suffering for months or years from chronic angina pectoris and who suddenly experience an aggravation of their complaints, that is, the attacks are more prolonged and more painful, they are produced by minimal efforts or occur at rest, and they are not relieved or are incompletely relieved by nitroglycerin. These conditions are suggestive of an impending infarction. We think that the term "evolutive angina pectoris due to subacute coronary insufficiency" would well define those conditions in which there is a critical increase in myocardial hypoxia but without definitive tissue damage.

In these cases active therapeutic measures must be taken, comparable to those taken in cases of acute coronary thrombosis. Complete bed rest for a minimum of 2 weeks is required, followed by a period of prolonged rest at home. A low caloric diet is advisable in order to reduce the metabolic needs; emotional factors must be avoided. Anticoagulant therapy with a Dicoumarin derivative or phenindione is indicated, with frequent controls of the prothrombinemia, which should be maintained at about the level of 25 per cent. This therapy is usually continued for several months after the evolutive phase has subsided. In some cases permanent anticoagulant therapy over an indefinite period of time may be indicated. The object of the anticoagulant treatment is to assure to the patient a relative protection against impending coronary thrombosis. However, because of its dangers, the permanent use of anticoagulants must not be prescribed routinely, but reserved for a few chosen cases. Oxygen therapy is necessary, by tent or by nasal tube. At first, oxygen is given permanently, and then after a few days it is discontinued at night. Sedatives are administered orally or rectally. Alcohol (brandy or whisky) may be helpful, about 20 to 30 ml. two or three times a day. Opium and its derivatives may be required during the first days in order to help the patient through this trying phase of his disease. The presumably vasodilating drugs are given routinely in high doses. Actually, it is difficult to determine which of these various therapeutic measures are responsible for the patient's improvement. Personally, we are inclined to think that oxygen therapy, opiates, and sedatives are the most effective agents in these conditions.

When the subacute phase has subsided, the patient is allowed to get up, then to go out, and lastly to resume his work after a convalescence of 3 to 6 weeks. The medications are discontinued gradually.

The course of subacute evolutive angina pectoris is variable. It may lead to chronic angina pectoris, which has been considered in the previous section; it may end in acute myocardial infarction; or, lastly, it may develop into "status anginosus," intractable angina pectoris with which we will now be concerned.

Intractable Angina Pectoris.—Intractable angina pectoris is characterized by repeated anginal attacks which occur on minimal effort or emotion, at rest, during the night, and sometimes without any apparent reason. These attacks are usually relieved by one or two tablets of nitroglycerin. In severe cases the frequency of attacks is such that the patients, living in constant dread of their recurrence and unable to perform the least activity, become complete invalids and often sink into drug addiction. The main features of this condition are its tenacity and its resistance to all the usual therapeutic measures. It is in these cases, which are fortunately rare, that the "heroic" methods, surgery and induced myxedema, are indicated after failure of all the common medical methods.

Two simple, anodyne procedures may be proposed as a first step: Novocain infiltration of the preaortic plexus or ligation of the internal mammary arteries under local anesthesia. If one of these procedures fails, or if its effects wear out, the second one may be subsequently attempted.

If angina pectoris is not improved by either of these methods, the creation of therapeutic hypothyroidism by radioactive iodine may be proposed. If this fails, one may have recourse to a surgical method of revascularization, without concealing its operative risk and the uncertainty of its results. At the present time we recommend the method of de-epicardialization of Harken[19] or the Beck-I operation. If this surgical attempt fails also, an operation for cardiac "denervation" may be considered as a last recourse; bilateral posterior rhizotomy seems the most likely to radically interrupt ischemic pain.

This way of proceeding, step by step, seems the most rational in these trying cases. Actually, it is very difficult to obtain from the patients the cooperation and trust necessary to achieve a methodic therapeutic schedule. These patients, tortured by their disease, are difficult to handle. They search desperately for relief and go from one cardiologist to another, from a physician to a charlatan, accepting the most incredible treatments and trying incoherently all the new drugs loudly praised in the press. Thus, very few cardiologists have been able to acquire sufficient experience with any of these "heroic" methods for the treatment of "intractable" angina pectoris.

SUMMARY AND CONCLUSIONS

Nitroglycerin remains the sole treatment of the anginal attack. Prophylactic therapy is related, in the majority of cases, to the cause of the underlying disease, namely, coronary atherosclerosis. Thus, it cannot be claimed that a real prophylactic treatment of angina pectoris has been discovered as long as its basic causes remain unknown and a method is not found to arrest its development and produce regression of the existent lesions. Nevertheless, in spite of these gaps in our knowledge of the fundamental disease, useful medical help can and must be offered to the coronary patients. To simplify didactically the

therapeutic problems, patients can be divided into three groups which are easily differentiated on clinical grounds.

1. In the group with chronic, inactive angina pectoris with a fixed level of diminished coronary reserve, ***not one*** medication has plainly demonstrated its general effectiveness or benefit. The main features in the management of these patients are the adoption of a new way of living void of haste, agitation, and emotional stress, the acceptance of a few limitations such as the quantitative and qualitative reduction of the caloric intake, the suppression of tobacco, and, above all, the peaceful comprehension and acceptance by the patient of his chronic disease. The willingness of the patient to establish with his disease a sort of *modus vivendi* is for him the most certain token of longevity.

2. In the group with severe, evolutive angina pectoris due to a more or less intense and prolonged subacute coronary insufficiency, the patients must be treated as if they had a myocardial infarction—complete bed rest, oxygen therapy, anticoagulants, opiates, and sedatives. Actually, an acute coronary thrombosis may occur during this phase of impending infarction; the evolutive phase may subside in a few weeks or months; or, in rare cases, he evolutive phase may persist and develop into intractable angina pectoris.

3. The group with intractable angina pectoris, in which the coronary reserve is hardly sufficient for the minimal metabolic needs of life, is characterized clinically by a chronic status anginosus. It is the invalids of this group who may benefit from the so-called "heroic" treatments of angina: surgical myocardial revascularization, production of a hypothyroidism by radioactive iodine, or even, as a last recourse, cardiac denervation by various procedures, the most effective apparently being the bilateral section of the upper four thoracic spinal roots.

It can be concluded that the management of angina pectoris is radically different according to the phase, inactive or active, of the atherosclerotic coronary process. In the inactive phase, characterized by a simple, chronic angina, the role of the physician is mainly to restore confidence and to lay out a few adequate rules of life, without loading the patient with medical prescriptions of doubtful efficacy. The cases of evolutive cardiac ischemia characterized by an aggravation of the symptoms, or the cases of chronically severe angina pectoris give rise to difficult and entirely different problems which must be solved according to each individual case. Thus, all the wisdom and experience of the physician are required to handle some truly distressing situations and to determine his choice between the numerous therapeutic methods available. Nothing less than the life, or at least the life expectancy, of the patient depends upon his decision.

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Special Article

A Semiquantitative Histopathologic Method for the Study of the Entire Heart for Clinical and Electrocardiographic Correlations

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In the last eight years we have evolved a gross and histopathologic method for the study of the entire heart, which we think will prove useful for electrocardiographic correlation. The gross method borrows liberally from prevailing methods; hence, a brief summary is necessary of the methods employed, past and present, in opening a heart at autopsy, and studying it subsequently. Such methods are either general, for the study of all structures, or special, for the study of individual structures such as the coronary arteries, the myocardium, or the conduction system.

GENERAL OR ROUTINE TECHNIQUES FOR THE OPENING AND THE STUDY OF THE HEART AT AUTOPSY

General methods for opening the entire heart at autopsy have been devised by Marjolin,[1] Virchow,[2] Rokitansky,[3] Wilson,[4] Zenker,[5] Mönckeberg,[6] Vermes,[7] and Kadletz.[8] Since many of these have been slightly modified by others, we will describe the various methods for opening each individual chamber.

Right Atrium.—The methods described for opening the right atrium are the following: (1) An incision is made joining both caval orifices with an extension into the atrial appendage (Mallory,[9] Farber[10]). (2) An incision is made along the lateral wall from a point between both venae cavae to the right atrioventricular (A-V) groove (Virchow,[2] von Gierke,[11] Rokitansky,[3] Chiari[12]). (3) An incision is made along the lateral wall from the A-V groove into the superior

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This investigation was supported by a research grant (H-3440) from the National Heart Institute, U. S. Public Health Service.

Received for publication March 19, 1959.

vena cava (Zenker,[5] Hauser,[13] Roessle[14]). (4) An L-shaped cut is made, one leg extending into the appendage from a point between both venae cavae, and the other extending at right angles to the first into the superior vena cava (Marjolin,[1] Cruveilhier,[15] Hyrtl[16]). (5) An inverted T-cut is made, the horizontal limb running above the A-V groove, and the vertical limb extending between both venae cavae (Wilson[4]). (6) An incision or combination of incisions is made opening the chamber from the posterior aspect (Ruge,[17] Nuhn[18]), and including the caval orifices (Braus[19]). (7) A transverse incision is made on the anterolateral wall distal to the caval orifices, distal to and in the vicinity of the sulcus terminalis (Kadletz,[8] Bischoff-Rüdinger[20]). (8) A series of incisions forming a window is made in the anterolateral wall (Bardeleben[21]). (9) An incision is made beginning in the inferior vena cava and passing through the lateral and the anterior walls of the atrium into the right atrial appendage (Mönckeberg,[6] Oppenheimer[22]). (10) A vertical incision is made extending from the anterior wall of the right ventricle through the tricuspid valve and the anterior wall of the right atrium, medial to the appendage ending in the superior vena cava (Vermes[7]).

Right Ventricle.—The right ventricle has been opened in the following ways: (1) A V-shaped cut is made, one limb of which runs along the margo acutus to the apex, or proximal to it (Marjolin[1]), and the other limb passes from the first cut at or near the apex paraseptally through the pulmonary artery (Marjolin,[1] Rokitansky,[3] Chiari,[12] Mönckeberg,[6] Bardeleben,[21] Hyrtl,[16] Ruge,[17] Braus,[19] Saphir[23]). (2) The first limb of the V-cut is as described above, but the second limb passes through the anterior wall of the right ventricle, from the first cut into the pulmonary artery (middle pulmonary cut) (Marjolin,[1] Virchow,[2] Kadletz,[8] Farber,[10] von Gierke[11]). (3) Both limbs of the V-cut are paraseptal in the anterior and posterior walls (Wilson,[4] Conference Group[24]). (4) A transverse section is cut through the mid-portion of the ventricles and is combined with the paraseptal and margo acutus cuts, starting from the original cut (Zenker,[5] Hauser,[13] Roessle[14]). (5) An inverted arched cut is made instead of a V-cut as in (1) (Weisse[25]). (6) The pulmonary artery and valve are opened first by a cut passing through the anterior wall of the right ventricle to the margo acutus, care being taken to preserve the valve cusps and the anterior papillary muscle. The tricuspid valve is opened from the anterior aspect of the heart by an incision going through the crista supraventricularis, the anterior wall of the right ventricle, and right atrium medial to the appendage, and ending in the superior vena cava (Vermes[7]).

Left Atrium.—The left atrium has been incised in the following manner: (1) An incision is made joining the pulmonary vein orifices with or without extension into the atrial appendage (Mallory,[9] Farber[10]). (2) An incision is made on the lateral border of the chamber from the mitral ostium into one or both left pulmonary veins (Chiari,[12] Rokitansky,[3] Zenker,[5] von Gierke[11]). (3) An incision is made between the pulmonary vein orifices in a transverse direction (Marjolin,[1] Virchow[2]), or from between the pulmonary vein orifices in an oblique direction extending into the appendage (Braus[19]). (4) An incision is made from between the left pulmonary veins in a direction perpendicular to the A-V groove (Mönckeberg[6]). (5) An incision is made vertically between the pulmonary

veins (Lauth,[26] Ellis,[27] Weisse,[25] Ruge,[17] Cruveilhier[15]). (6) A window may be cut in the anterolateral wall (Hyrtl,[16] Bardeleben[21]). (7) An inverted T-cut may be used, the horizontal limb running parallel to the atrioventricular border (Wilson[4]). (8) An incision is made from the anterior wall of the left ventricle extending cephalad through the anterior mitral leaflet and anterior wall of the atrium medial to the appendage (Vermes[7]). (9) A curved incision is made along the junction of the appendage and the atrium, one end directed toward the aorta, and the other toward the left border of the heart (Kadletz[8]).

Left Ventricle.—The left ventricle is usually opened by a V-shaped incision as follows: (1) One limb of the cut extends along the margo obtusus to the apex, while the other passes paraseptally through the aortic valve from the apex. This cut passes between the pulmonic valve and the left atrial appendage (Marjolin,[1] Virchow,[2] Bischoff-Rüdinger,[20] Bardeleben,[21] Conference Group,[24] Mönckeberg,[6] Mallory,[9] Maresch and Chiari,[28] Chiari,[12] Farber,[10] Saphir[23]). (2) The first cut is as described above, but the second cut transects the septum and posterior wall of the pulmonary conus (Cruveilhier,[15] Heschl,[29] Rokitansky,[3] Chiari[12]). (3) In addition to the cuts in (1) a frontal cut is made through the septum (Ruge,[17] Braus[19]). (4) In addition to the first cut in (1) the second cut passes through the midpoint of the margo obtusus across the anterior wall of the left ventricle into the aorta (Pokrowsky[30]). (5) The margo obtusus and paraseptal cuts start from a transverse cut placed midway between the apex and base of the ventricles (Zenker,[5] Hauser,[13] Roessle[14]). (6) Paraseptal cuts are made along the anterior and posterior longitudinal sulci, separating the anterior and posterior walls from the septum (Wilson,[4] Hyrtl,[16] Weisse[25]). (7) The left ventricle is opened from the aorta to the apex, the incision passing between the right and left cusps of the aortic valve. The mitral valve is then opened by an incision extending cephalad from the first, at about its midpoint, through the anterior mitral leaflet and anterior atrial wall medial to the appendage (Vermes[7]). (8) The left ventricle is opened by the usual margo obtusus incision. Through the first incision the intact anterior mitral valve leaflet is then incised at its midpoint, and the incision carried into the aortic valve between the right and left cusps. By this method only one external cut is made into the ventricle (Kadletz[8]).

SPECIAL METHODS FOR THE STUDY OF INDIVIDUAL STRUCTURES

1. *Techniques for the Examination of the Myocardium in Particular.*—Kossmann and de la Chappelle[31] first opened the heart in the Virchow way, then fixed and resutured it. Following this they examined the coronary arteries by transverse incisions, 0.5 cm. apart, and made a diagrammatic pictorial representation of the lesions so discovered. The heart was then cut into transverse sections, 1 cm. thick, by means of a rotary slicer, and multiple microscopic sections were used to confirm the gross diagnosis. Myers and associates[32] employed a radiopaque injection technique, modified from Schlesinger,[33] to examine the coronary system, and, after fixing the heart, dissected the atria from the ventricles, opening the latter by transverse serial slices, 1 cm. thick. These slices were placed on a cassette in a prearranged order and roentgenograms were taken. All evi-

dent suspicious or grossly diseased areas were examined by full-thickness ventricular blocks. When a lesion was suspected by any of the three procedures, ECG, injection, or gross study, a series of blocks was taken around the circumference of the ventricles at one or more levels. The location of all microscopic sections was marked on the roentgenograms, and the coronary arteries were opened by multiple transverse sections to check the x-ray findings. Lowe,[34] and Wartman and Souders[35] used a series of transverse slices through the myocardium of infarcted hearts, correlating the location of the infarcts or scars with the patterns of the cardiac muscle bundles.

Recently, Sayen, Sheldon, and associates[36,37] elaborated a two-stage procedure for studying the myocardium. The first consideration was the creation of a pictorial record of the myocardium obtained by serial transverse slicing of the ventricles and a set of drawings of the slices showing the location of damaged areas, the lesions of different ages being represented by varieties of shadings. Following this pictorial record they devised a schema, or myocardial map, of the ventricles by which data accumulated from the slicing technique and recorded by sketches of the slices could be graphically presented with as much precision as necessary. For purposes of their study, the right ventricle and both atria were excluded from this map, which consisted of three shield-like structures representing diagrammatically the anterior wall, septum, and posterior wall of the left ventricle. In a later publication the authors describe a corollary to the pictorial record and myocardial map. This is a linear chart illustrating schematically the location and extent of myocardial damage in a number of hearts. The three segments of the left ventricle are divided into 24 areas, which are then projected horizontally on a chart. The lesions occurring in any of these areas are illustrated by appropriate hatching which varies according to the age and extent of the damage. By means of this linear chart a diagram of the myocardial damage in a number of hearts could be represented schematically on a single page, and correlation of hearts showing similar types of damage could be easily obtained. The main coronary arteries and any lesions in them were also represented schematically, and the 24 areas of the myocardium were arranged linearly in such a fashion that areas supplied by the same artery were in juxtaposition. As a result, the complete pattern of myocardial and coronary artery damage in any given heart was concisely and accurately represented. To complete the study, relevant blocks of tissue were taken for microscopic examination, their location and orientation being accurately recorded on the initial pictorial record of serial slices.

2. *Techniques for the Examination of the Coronary Arteries.*—The most commonly employed routine method of examining the coronary arteries is the use of multiple transverse sections of the main branches or of all visible branches. Such methods were used by Friedberg and Horn[38] and Gross and Sternberg.[39] Some workers advise a combination of longitudinal opening and transverse sectioning. Saphir and associates[40] used dissection exclusively in order not to dislodge thrombi. Schlesinger[33] felt that no matter how careful the dissection, some branches would be missed.

Injection techniques for examination of the coronary arteries have been done for many years. Hyrtl,[41] in 1855, used a metallic alloy and followed this with corrosion. Many corrosion techniques have been elaborated since then, but from the pathologist's point of view all have the great disadvantage of destroying the myocardium and valves. Spalteholz[42] injected the arteries with gelatin in which were suspended various minerals or other opaque substances, fixed the hearts, then bleached and cleared them in the manner of histopathologic technique for microscopic blocks of tissue. Gross[43] injected a suspension of barium sulfate in warm gelatin, fixed the heart, then took stereoscopic x-rays. Because the overlap due to the various planes of the heart made interpretation difficult, Gross and Kugel[44] modified the original method by slicing the heart after injection and fixation, and taking x-rays of the slices. Crainicianu[45] and Campbell[46] used a similar technique. Schlesinger[33] considered all of these techniques to have some deficiencies and devised an injection dissection technique which involved the use of a suspension of lead phosphate in agar, colored differently for the right and left coronary arteries. The mass was injected at a pressure of 150 mm. Hg, at 45°C., and the heart was opened in such a manner that the coronary arteries were unrolled into one plane for radiography. Following radiography, the colored coronary tree was completely dissected. In 1947, Prinzmetal and associates[47] perfused the heart with radioactive erythrocytes and glass spheres of known diameter and thereby demonstrated the existence of anastomoses between the coronary arteries and ventricles, between the coronary arteries themselves, and between the coronary arteries and veins.

3. *Techniques for the Study of the Conduction System.*—In order to study the conduction system histologically, Oppenheimer,[22] Mönckeberg,[6] and Kadletz[8] made some modifications in the gross technique of opening the heart. To keep the sinoatrial (SA) node intact, Oppenheimer opened the right atrium by a cut from the inferior vena cava to the right atrial appendage. This modification was adopted by Mönckeberg. Kadletz devised a method of opening the entire heart to keep the conduction system intact. A transverse cut is made in the right atrium parallel to the base of the heart, distal to the sulcus terminalis, starting medially near the tip of the appendage, and not compromising either caval orifice. From its lateral end a second incision is made along the margo acutus to the apex of the right ventricle. A mid-pulmonary cut is then made, not disturbing the anterolateral papillary muscle. The left atrium is cut by a vertical curved incision where the atrial appendage joins the atrium, one end directed toward the aorta, and the other end toward the left border of the heart. The left ventricle is then opened along the margo obtusus by a continuation of the previous cut, care being taken to cut the posterior mitral valve leaflet exactly in the midline so as to preserve the papillary muscles. The final incision passes exactly through the middle of the anterior mitral leaflet through the commissure between the right and left aortic cusps into the aorta.

Various techniques have been evolved for the histologic and histopathologic examinations of the conduction system. These techniques concern themselves mostly with methods of sectioning, although there has been some variation in methods of fixation, embedding, and staining.

Early authors who studied the A-V node, bundle, and bundle branches cut out a block comprising the lower atrial and the upper ventricular septum. This block was either left in toto or subdivided into several blocks. These blocks were embedded in paraffin or celloidin. Serial sections were cut in a plane horizontal or vertical to the ventricular septum, from 7 to 20 microns thick. All or every fifth to tenth section was stained by hematoxylin-eosin, van Gieson, or Mallory (Braenig,[48] Tawara,[49] Fahr,[50] Mönckeberg,[51] Rénon and Géraudel,[52] Flemming and Kennedy,[53] Draper,[54] Cohn,[55] Nuzum,[56] Wilson and Grant[57]). Mönckeberg and Rénon and Géraudel stressed the importance of elastic tissue stains in differentiating these structures, and the former studied the reticular pattern. Mahaim[58] crystalized the preceding methods into a standard method. Although he originally used a vertical orientation in his cutting, he eventually decided in favor of the horizontal method. He divided the lower part of the atrial and the ventricular septum up to the anterior papillary muscle of the right ventricle into three to five blocks by horizontal cuts at right angles to the long axis of the heart. The first block contained the A-V node and atrial connections, the A-V bundle, and the beginning of the bundle branches. The other blocks contained the remainder of the bundle branches. Serial sections were cut in a horizontal manner at 8 to 10-micron thickness. All sections were retained separately and labeled. Every fifth, tenth, or twentieth section was stained with trichrome. Other sections were stained whenever necessary. This technique was followed by others in succeeding years, with or without modifications (Lenègre, Deglaude and Hazim,[59] Lenègre and Chevalier,[60] Langeron, Giard and Destombes,[61] Lenègre, Chevalier and Jacquot[62]). Yater and his associates,[63-66] employing serial sections, at times used a vertical technique and at times a horizontal. In some cases the A-V node, bundle, and the beginning of the bundle branches were sectioned vertically, while the remainder of the bundle branches were sectioned horizontally. In one type of modification the block containing the A-V node, bundle, and bundle branches comprised the entire thickness of the septum, while the other blocks contained half the thickness of the septum, in which was found the right or left bundle branch. Serial section techniques were also employed by Cordero,[67] Swift and Smith,[68] Evans and Turnbull,[69] Porto,[70] Bischoff,[71] Castoldi,[72] Sanabria,[73] Coakley,[74] Rondolini,[75] Blair and Davies,[76] Copenhaver and Truex,[77] Stotler and McMahon,[78] Robb, Kaylor and Turman,[79] Baird and Robb,[80] and Nonidez.[81] In addition, Blair and Davies, Nonidez, Field,[82] Tcheng,[83] Davies, Francis and King,[84] and Rossi[85] used silver stains for the study of nerve and specific tissue.

In 1951, Lenègre and Chevalier,[86] and Lev, Widran and Erickson[87] independently evolved simplified routine methods of studying the A-V node, bundle, and branches. In the method of Lenègre and Chevalier, a block is fashioned as follows: The posterior cut of the block lies at the orifice of the coronary sinus. The anterior cut is parallel to the first, anterior to the bundle. The proximal cut is above the orifice of the coronary sinus, and the distal cut is at the base of the anterior papillary muscle. This block is fixed in neutral formalin (which is changed every 48 hours) under vacuum for 3 to 10 days. The block is embedded in paraffin and sectioned vertically from the posterior aspect anteriorly,

or vice versa. All sections are retained in separate bottles. For routine purposes, every twentieth or fortieth section is stained with hematin-alcoholic floxine-safranine. Other sections are later stained when needed. This gives a total of 50 to 120 sections in routine cases. Botti and Visioli,[88] and Rossi[85] have adopted this method of study. The method of Lev, Widran and Erickson is described below with modifications. Carbonell[89] has adopted this method of sectioning for cholinesterase studies.

The SA node has been studied by serial section technique by Koch,[90] Schonberg,[91] Hedinger,[92] Flemming and Kennedy, Draper, Cohn, Yater, Mahaim, Swift and Smith, Bischoff, Fiorio,[93] Coakley, Blair and Davies, and Copenhaver and Truex. Recently, Lev and Watne[94] devised a simplified routine method for the study of the SA node. This method is described below with modifications. This method was adopted by Botti and Visioli.

An isolated section technique for the study of the conduction system was used by Rosenthal.[95] He studied the SA node, the atrial musculature, and the A-V node, bundle, and bundle branches. However, the above review reveals that there is no comprehensive method for the study of the entire heart to be used for electrocardiographic correlation. Such a study should include the SA node, the approaches to the SA node, the atrial musculature, the approaches to the A-V node, the A-V node, the A-V bundle, the bundle branches up to the papillary muscles, and the ventricular myocardium. For, in the larger sense, the entire heart is a conducting mechanism. Also, this method should be semiquantitative. A truly quantitative method would entail serial sections of the entire heart, which is an impossibility as a routine method, and difficult as a research method. The method to be described was thus evolved with the aforementioned concepts in mind.

HISTOPATHOLOGIC METHOD FOR ELECTROCARDIOGRAPHIC CORRELATION

The heart is removed with the lungs as a unit, by whatever method the prosector is accustomed to. The heart is placed on the table, with the anterior surface facing the prosector. The first cut passes from the left margin of the circumference of the opening of the inferior vena cava through the anterior wall of the right ventricle in an oblique manner through the right atrial appendage up to its highest point (Fig. 1). Care is taken not to approach in any way the linea terminalis of the right atrium. The second cut is made from the first cut through the right atrium and ventricle along the margo acutus up to the apex. The third cut passes from the second cut through the anterior wall of the right ventricle along a line directly proximal to the anterolateral papillary muscle, into the pulmonary artery. The pathologic change of the right side of the heart is then surveyed (Fig. 2). Next, the heart and lungs are turned to the posterior surface, and a nick is made in the left atrial wall just distal to the entry of the left pulmonary veins. Cut 4 commences in this nick and passes along the proximal portion of the atrium horizontally to the right pulmonary veins (Fig. 1). This cut may be extended now or later into the four pulmonary veins. Cut 5 is made from a point in Cut 4 through the left atrium and ventricle along the obtuse

margin of the heart to the apex, just between the anterior and posterior groups of papillary muscles. Cut 6 passes from Cut 5 at the apex, paraseptally to the base. As it passes through the aortic valve, the cut lies between the pulmonic valve and the left atrial appendage. It continues along the anterior (ventral) wall of the aorta in a curved manner between the exit of the brachiocephalic arteries and the attachment of the ligamentum arteriosum. Cut 6 meets the cut made in the aorta in the en-masse or en-bloc dissection technique. If no such cut has been made previously, then Cut 6 is extended into the descending aorta along the previously mentioned line. The left side of the heart may now be inspected for pathologic change (Figs. 3 and 4). All observations may now be recorded on the protocol, but no further cuts are made in the heart at this time. The heart and aorta are now separated from the lungs. The coronary arteries are opened by dissection if a lumen is visible. Where a lumen is not visible, cross sections are cut every ¼ of an inch. The circumflexes, descending arteries, the ramus anterior ventriculi sinistri, and the ramus obtusi are routinely opened. The

A. *B.* *C.*

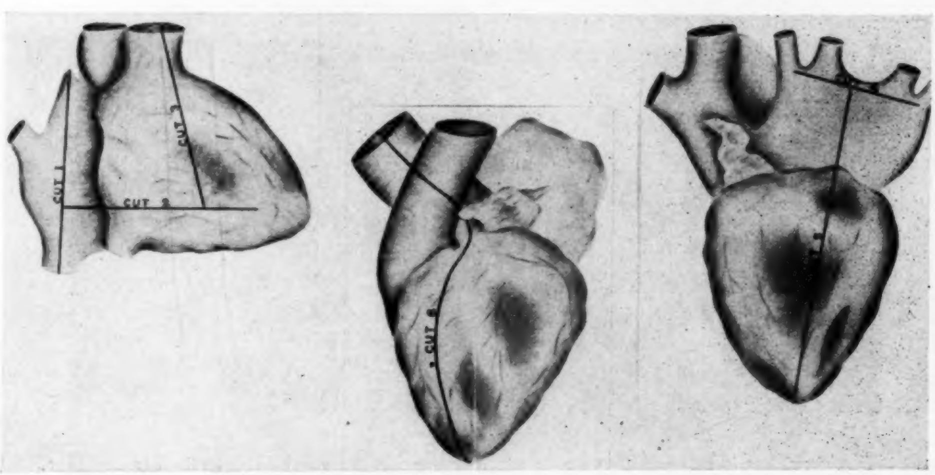

Fig. 1.—Three views of the heart depicting the various cuts for opening the heart described in the text. *A*, Anterior surface of the heart. *B*, Anterior surface of both ventricles. *C*, Left atrium and left ventricle.

ostium of the right coronary artery may be opened at this time, cutting through the aorta, or it may be gently probed and cut later. The aorta is now cut ½ inch above the sinuses of Valsalva, and the heart with the attached base of the aorta is weighed. If the pathologic change is such as to warrant keeping the aorta with the heart, then the heart may be weighed, holding the aorta loosely above it. Now various measurements of thickness of walls and size of chambers are made; these measurements are being studied at the present time and will be published later.

The heart is packed with cotton in all chambers and orifices, and fixed in 10 per cent neutral formalin (4 per cent formaldehyde) for 2 to 7 days, at the end of which time the heart is weighed again and all chambers are photographed. The

second stage of the cutting of the heart may now be instituted. The aorta is cut off at the upper margin of the sinuses of Valsalva (if it has not previously been cut), and the right coronary ostium is now opened if it has not been opened before. The block containing the SA node is now fashioned. This is done by a cut (Cut 7, Fig. 5) along the proximal margin of the right atrium through the superior vena cava. The next cut (Cut 8, Fig. 6) extends the original cut through the atrial appendage over the hump for a distance of about ½ inch into the superior wall. The final cut to form this block extends from the end of the previous cut along the superior wall of the right atrium to meet the first cut (Cut 9, Fig. 6) (Fig. 7,*a*). This block is weighed. The next block to be fashioned contains the blood supply to the SA node, the ramus ostii cavae superioris. This block consists of the distal portions of the anterior and lateral walls of the right atrium.

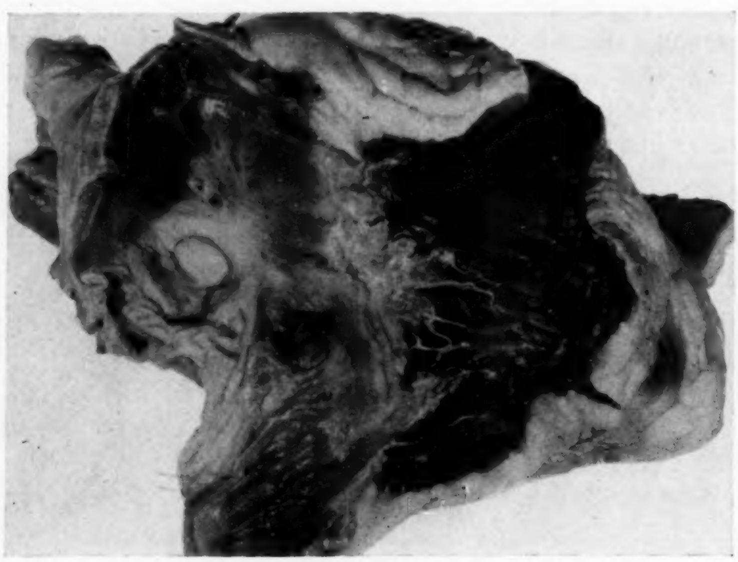

Fig. 2.—View of right side of the heart as opened in the method described in the text.

To fashion it, the ostium of the right coronary artery is excavated from its bed and a cut is continued from here along a line distal to the right circumflex coronary artery, passing through the fat in the right A-V ostium but not through the entire wall. The wall proximal to the tricuspid valve is now cut through. The cut that completes the block passes through the roof of the right atrium adjacent to the septum to meet the distal cut (Fig. 7,*b*). This block is weighed.

The parietal walls of the right and left atria and ventricles are now separated from the atrial and ventricular septa and are weighed (Fig. 7). To fashion the block containing the approaches to the A-V node, and the A-V node, bundle, and bundle branches, we proceed as follows: A cut is made along a line just posterior to the moderator band and the right anterolateral papillary muscle at an angle of almost 45° to the septal band of the crista supraventricularis (Cut 10, Fig. 8). This serves as a base line for the formation of the block. A second

oblique cut is then made in the upper aspect of the atrial septum from the root of the aorta through the center of the fossa ovalis (Cut 11, Fig. 8). A third cut is made at right angles to the first cut, along a line proximal to the insertion of the Eustachian valve so that the coronary sinus region is in the block as well as the crux—the junction of the right circumflex coronary with the posterior

Fig. 3.

Fig. 4.

Fig. 3.—View of left atrium and inflow tract of left ventricle as opened in the method described in the text.
Fig. 4.—View of outflow tract of left ventricle as opened by the method described in the text.

descending branch (Cut 12, Fig. 8). A fourth cut is made through the lower part of the arch of the crista parallel to the base line, making sure that the base of the aorta and most of the pars membranacea is in the block (Cut 13, Fig. 8).

Fig. 5.

Fig. 6.

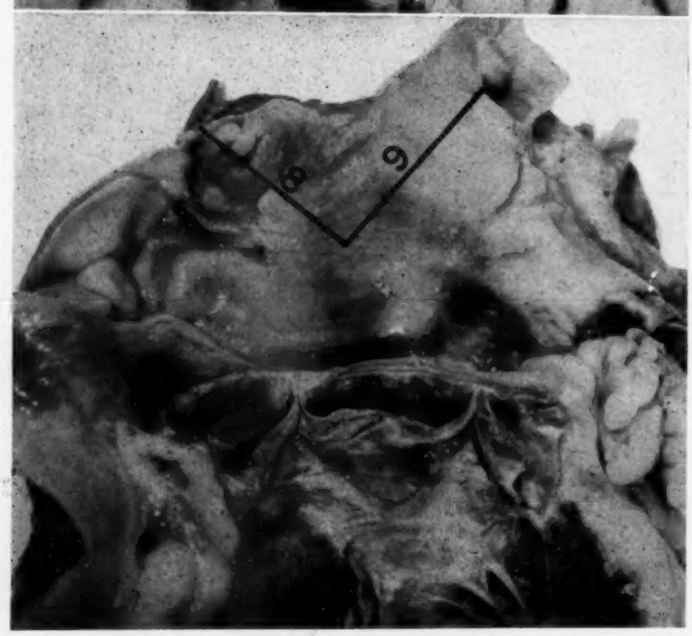

Fig. 5.—View of sinoatrial nodal region. Cut 7 is described in the text.
Fig. 6.—Superior wall of both atria. Cuts 8 and 9 are described in the text.

This produces a block containing the A-V node, A-V bundle, right bundle branch, and the proximal portion of the left bundle branch, including the approaches to the A-V node and the blood supply to the A-V node and bundle—the ramus

septi fibrosi (Figs. 8 and 9). This block is then further subdivided as follows: A cut is made along a line parallel to Cut 2 through the pars membranacea, proximal to the insertion of the tricuspid valve on the pars membranacea (Cut 14, Fig. 8). This produces block *G* (Fig. 10). Another cut is made parallel to the previous cut, along a line passing through the muscle of Lancisi (Lushka) (Cut 15, Fig. 8). This produces block *H* (Fig. 10). The remainder of the original

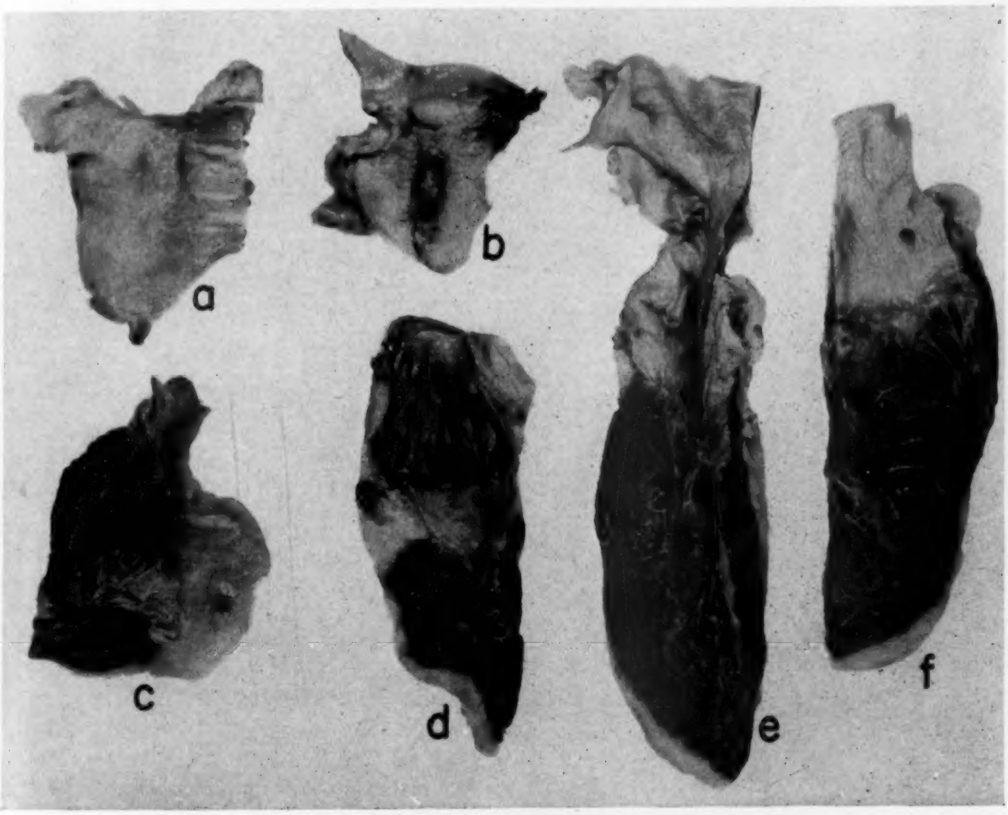

Fig. 7.—Parietal portions of the heart. ***a,*** **Sinoatrial nodal region, external view.** ***b,*** **Block containing blood supply to sinoatrial node, external view.** ***c,*** **Anterior wall of right ventricle, internal view.** ***d,*** **Posterior wall of the right atrium and ventricle, internal view.** ***e,*** **Anterior wall of the left atrium and ventricle, internal view.** ***f,*** **Posterior wall of the left atrium and ventricle, internal view.**

block is further subdivided according to its thickness into two or more blocks (*I, J, K,* Fig. 10) (Cut 16, Fig. 8). Block *G* thus contains the A-V node, penetrating portion of the bundle, the beginning of the branching portion of the bundle, the approaches to the A-V node, including the coronary sinus region, and the ramus septi fibrosi. Block *H* contains the remainder of the branching portion of the bundle, the bifurcation, and the beginning of the right and left bundle branches. The remainder of the blocks (*I, J, K*) contain the remainder of the right bundle branch and the remainder of the proximal portion of the left bundle branch. Block *H* is now further subdivided into two blocks (*HA* and *HB*) along a line just distal to the distal angle of the pars membranacea. The myo-

cardium, during this process of cutting, is examined on the cut surfaces, and a second report is made, which finishes the second phase of the examination of the heart. The entire heart so subdivided may then be stored in neutral formalin for the final histologic examination.

Fig. 8.

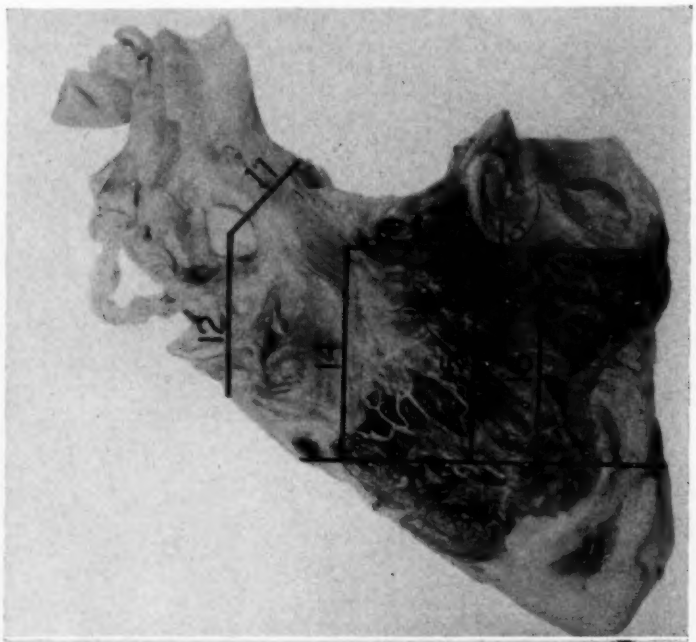

Fig. 9.

Fig. 8.—Atrial and ventricular septum, right side. Various cuts are described in the text. Note: Cut 13 actually reaches Cut 12, but behind the triangle of muscle beneath and to the left of Cut 11.

Fig. 9.—Atrial and ventricular septum, left side. Boxed-in area contains the atrioventricular node, bundle, the right bundle branch, and part of the left bundle branch.

In the final phase of the examination of the heart the atrial segments are separated off from the parietal walls of the ventricles just above the A-V valves. The parietal walls of the ventricles are then weighed. The weight of the atrial walls can be deduced from previous weights of the entire parietal walls and the weight of the block containing the blood supply to the SA node. We then proceed as follows. The base of the left anterior and posterior papillary muscles are cut out as blocks and are treated separately (see below). Likewise,

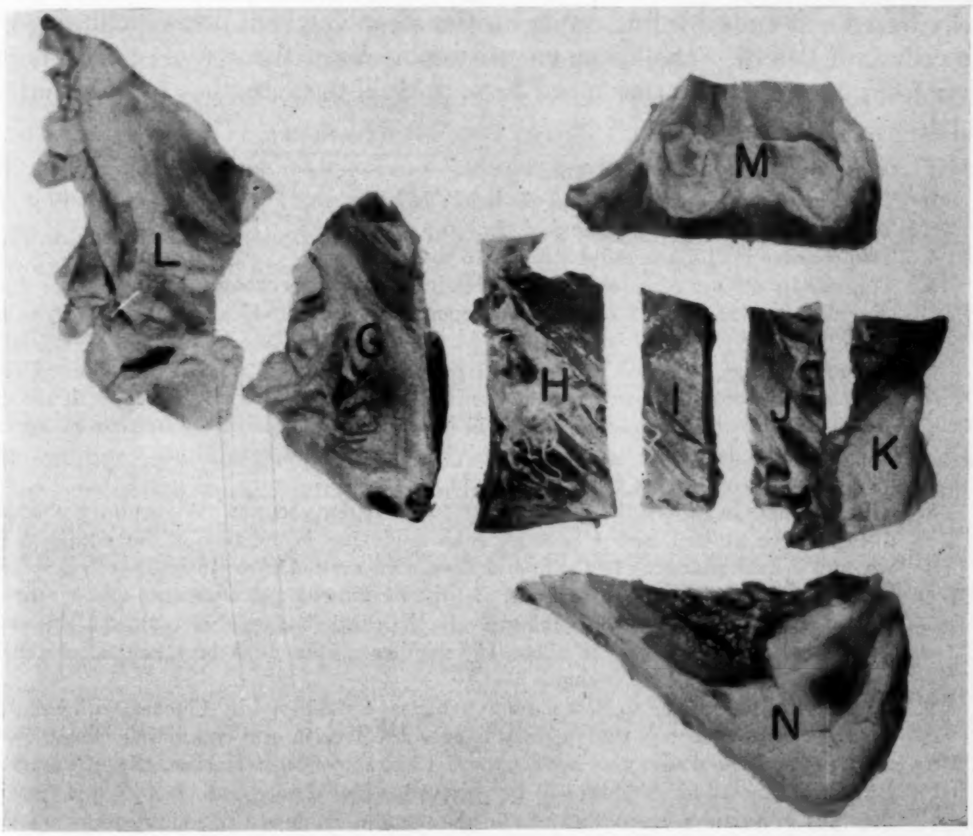

Fig. 10.—Various blocks obtained in cutting the atrial and ventricular septum. Blocks *G-N* are described in the text.

the postero-basal angle of the postero-apical portion of the septum is cut off and treated separately (see below) (Cut 17, Fig. 9). The remainder of each ventricular wall is now divided into two parts—a basal and an apical portion. Each of these portions is cut completely into blocks, ¼ inch in thickness and passing from endocardium to epicardium, with the long axis of the blocks corresponding to the long axis of the heart. The atria likewise are completely sectioned and placed in the bottles containing the corresponding basal portions of the ventricles. Blocks passing through the A-V rings include the corresponding valves. Similarly, the antero-basal (Fig. 10,*M*) and postero-apical (Fig. 10,*N*) portions of the septum are completely cut into blocks, as is the atrial septum proximal

to the A-V node (Fig. 10,*L*). Blocks passing through the aortic and pulmonic valves are shaped so that the section is at right angles to the annulus. Final comments are made in the protocol pertaining to this last phase of gross examination. These blocks may, of course, go through routine methods of embedding. Two sections are cut from each block and stained with hematoxylin-eosin and Weigert-van Gieson stains.

The other blocks of tissue (SA node, A-V node, bundle and bundle branches, blood supply to the SA node, and anterior and posterior papillary muscles) are dehydrated and embedded according to the schedule given below, following the procedure of Péterfi. The above-mentioned blocks of tissue must not be larger than 5 cm. in greatest dimension and 3 cm. thick; if they are, they must be further subdivided.

1. Wash in running water overnight.
2. Two changes in 80 per cent ethyl alcohol in 24 hours.
3. Two changes in 95 per cent ethyl alcohol, 6 to 8 hours.
4. Two changes in absolute ethyl alcohol, 16 to 20 hours.
5. Transfer to a 1 per cent solution of celloidin in methyl benzoate until the tissue sinks. (Usually, it takes from 12 to 24 hours, depending upon the thickness and density of the tissue.)
6. A second change in a fresh solution of 1 per cent celloidin in methyl benzoate. This is kept in from 3 to 30 hours, or 1 hour per millimeter of thickness. However, if the exigencies of time require a longer period in the second celloidin, the tissue can be kept in this solution indefinitely.
7. Three changes of benzene for 2 hours each.
8. Three changes in melted tissue mat at 56° to 58° under vacuum. A vacuum embedding oven may be utilized, and 1 hour for each millimeter is the time of embedding under vacuum in each change. In the first change, a vacuum of 10 to 15 inches of Hg is used, which is built up in 20 to 30 seconds. In the second change, a vacuum of 20 inches of Hg is used, and is built up in 1 minute. In the third change, a vacuum of 25 inches of Hg is used, and is built up in about 1½ minutes. Care must be taken to release the vacuum slowly after each change.
9. Transfer the tissue from the last paraffin to a glass container, 3 by 4 inches, with a slightly narrower base than top, and slightly lined with glycerin and containing melted tissue wax (56° to 58°). Leave this in vacuum of 15 inches of Hg for about 15 to 20 minutes. By this means all air bubbles will be removed. The glass container with the tissue is then put in a pan of ice-cold water and the paraffin is allowed to solidify to form a thin film of about 3 mm. Then the tissue is correctly oriented for cutting and the paraffin is allowed to solidify completely. The block is placed in a refrigerator for about 15 to 20 minutes. Then the glass container is turned upside down and the block is ready for trimming and sectioning.

The block containing the SA node and its approaches is sectioned as follows: The block is cut serially at 5 to 8-micron thickness, and every eightieth section is retained for six sections, and every twentieth section thereafter. The block containing the blood supply to the SA node is sectioned as follows: At this point, if the block is very large, it may be subdivided into two or three blocks by lines parallel to the acute marginal cut. Each of these blocks is sectioned with these latter cuts as base lines, at 7 to 8-micron thickness, and every eightieth section is retained. The sections are alternately stained with hematoxylin-eosin and Weigert-van Gieson stains.

Blocks containing the A-V node, bundle, and bundle branches are sectioned as follows: The point of sectioning begins along the line parallel to Cut 12. All of these blocks are sectioned serially at 6 to 8-micron thickness. In all blocks except *HA*, every twentieth section is mounted and stained. In block *HA*, every tenth section is so treated. All sections are stained alternately with hematoxylin-eosin and Weigert-van Gieson stains. In blocks containing the left papillary muscles, and in the block of the postero-basal triangle of the postero-apical portion of the septum, every fortieth section is mounted and stained. The total histologic study so done yields about 1,300 to 1,600 sections, and takes an average technician 6 weeks to 2 months to accomplish.

In sections which have been stained by the Péterfi method, the celloidin must be removed. This is done as follows: After the paraffin has been removed with zylol, the sections are placed in 100 per cent alcohol for 5 minutes. They are then placed in a mixture of equal parts of ether and absolute alcohol for 5 to 10 minutes. They then pass through 95 per cent alcohol, 80 per cent alcohol to running water, and are stained.

DISCUSSION

The above-described method of sectioning and sampling the entire heart yields qualitative data of changes in the atrial and ventricular endocardium, myocardium, and epicardium, the atrioventricular and semilunar valves, the entire conduction system, and the coronary arteries and veins. It yields semi-quantitative data of all but the valves, coronary arteries, and veins. It also localizes pathologic change in the ventricular myocardium according to wall and part of wall. It is self-evident that this method is not so good as some of the prevailing methods for the study of the myocardium or coronary arteries alone. It likewise cannot be used for the study of lateral wall infarcts. However, an attempt is made here to offer the most useful data for electrocardiographic correlation which is possible in a routine procedure. If this routine method seems too burdensome and lengthy, we feel it is still necessary to give a proper anatomic base for electrocardiographic interpretation.

SUMMARY

1. The prevailing routine and special methods of studying the heart grossly and histopathologically are reviewed.

2. A gross and histopathologic method of studying the heart especially for electrocardiographic correlation is described.

Acknowledgment is made to Mr. Ralph Alvarez, B.S., A.S.C.P., for introducing the Péterfi method in our laboratory.

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Book Reviews

VERHANDLUNGEN DER DEUTSCHEN GESELLSCHAFT FÜR KREISLAUFFORSCHUNG. 23 Tagung, Bad Nauheim vom 26. bis 28. April, 1957. Themen: Kreislauf in Narkose und Hypothermie. Angeborene Herzfehler. Edited by Prof. Dr. Rudolf Thauer, Darmstadt, 1957, Dietrich Steinkopff, 404 pages, 167 illustrations.

The twenty-third volume of the proceedings of the annual meeting of the Deutschen Gesellschaft für Kreislaufforschung is, like the preceding volumes, an excellent condensation of present cardiovascular research in Germany. The meetings, however, have a somewhat international flavor, with papers in the present volume from the United States (S. M. Sancetta, Cleveland, Ohio), England (G. R. Graham, London), Italy (V. Malamani, G. Pellegrini, and F. Campagnori, Pavia), Netherlands (A. G. Brom, Leiden), Czechoslovakia (I. Bor, Prague), and Sweden (L. Werkö, Göteborg). There were two main topics: circulation in anesthesia and hypothermia (first day of the meeting), and congenital heart disease (second day of the meeting). The third day was reserved for papers with a free selection of the topic. A total of 49 formal papers was presented, but, including the discussions, the title page lists 283 articles.

The topic of the first day is of particular interest because of new information and, in regard to hypothermia, recent clinical applications. R. Thauer gives a thorough review of the physiological basis of circulation in anesthesia (mostly barbiturates), based on animal experimentation, with emphasis on cardiovascular reflexes (pp. 3-32), while W. Brendel and C. Albers discuss the physiological basis of hypothermia (pp. 33-52). Sancetta presents the hemodynamic effects of anesthesia (pp. 61-78), and G. R. Graham, the circulation in hypothermia in man (pp. 79-100). There seems to be agreement that below a critical level of body temperature of 29°C. the risk of auricular fibrillation, ventricular tachycardia, or ventricular fibrillation is greatly increased, particularly in older individuals or in patients with heart disease. The changes in circulation during cooling and rewarming are not mirror patterns. Budelman and Lichtenauer (pp. 126-130) report a decrease in the intramuscular pressure during anesthesia as a factor contributing to the deterioration of the venous return. Electrocardiographic studies (animal experiments) in hypothermia were presented by W. Blasius and associates (pp. 135-142) and by E. Gudeman and K. Donat (pp. 142-147). In experimental cerebral ischemia the time of possible resuscitation increases about four times with a drop of body temperature from 37 to 23 degrees C., but is cut in half by cardiac insufficiency produced by tracheal occlusion (H. Hirsch, p. 148). The author concludes that cardiac insufficiency rather than cerebral ischemia is the limiting factor for resuscitation. H. Gillmann, in confirmation of other recent information, was unable to find any warning sign for the development of ventricular fibrillation in 100 cases of surgery during hypothermia.

The use of Lillehei's method of extracorporeal circulation in the systematic investigations in 38 dogs, in regard to oxygenation, general and pulmonary circulation, brain circulation (H. Meyer-Wegener and associates, p. 327), and the ECG (P. Schölmerich and associates, p. 335) is of great interest in view of its increasing use in cardiac surgery.

The papers mentioned are an arbitrary selection in view of the limited space for a book review; many of the other papers presented are of equal importance and interest.

The Pathology and Management of Portal Hypertension. By R. Milnes Walker, M.S., F.R.C.S., Professor of Surgery, University of Bristol. London, 1959, Edward Arnold, Ltd., 113 pages, 67 illustrations. In the U.S.A., Williams & Wilkins Co., Baltimore.

This monograph clearly reflects the surgical orientation of the author. It is concise, well written, adequately illustrated, and easily read. From the standpoint of the internist, it serves a useful purpose in providing a convenient and brief review of the surgical aspects of the pathophysiology and treatment of portal hypertension. Beyond these points, however, the coverage is altogether too brief. Regarding medical aspects of the topic, the book provides only slightly more than is well known to all of the medical subspecialties. To this end, the title is somewhat misleading in that there is no implication that the discussions of the management of portal hypertension and its complications in this monograph are predominantly surgically directed. Little, if any, attention is given to the newer, although unproved, aspects of medical therapy in these complications, some of which frequently are important adjuncts regardless of the type of therapy utilized. These include considerations such as cold water lavage, drug therapy (vitamin K, arginine, glutamate, Pitressin), and the finer details and problems in the use of the Sengstaken tube and blood transfusions.

Fundamentals of Electrocardiography and Vectorcardiography. By Lawrence E. Lamb, M.D., Director of Cardiology and Chief, Department of Internal Medicine, Air University, School of Aviation Medicine, USAF, Randolph Air Force Base, Tex.; Consultant in Cardiology, 3700th USAF Hospital, Lackland Air Force Base, San Antonio, Tex. Springfield, Ill., 1957, Charles C Thomas, 142 pages, 158 illustrations.

The book contains a good introduction to the vectorial concepts of electrocardiography and to the author's own method of vectorcardiography, which uses two perpendicular leads from points equidistant from a roentgenologically determined "cardiac center." A lead from a point directly overlying this center to the "central terminal" is used for the sagittal component. The amplification of each component is adjusted in each person individually according to the length of each lead, and convenient charts for this purpose are contained in the Appendix. Other methods of vectorcardiography are not discussed. A very useful table enables a rapid approximate determination of the spatial angle between any two cardiac vectors from their axes in the three conventional limb leads and their transition zones in the unipolar precordial leads. Some of the author's concepts concerning the electrophysiologic bases of the electrocardiogram deviate from the currently accepted ideas (for instance, those concerning ventricular repolarization or the effect of stroke volume and respiration on cardiac vectors), so that use of other electrocardiographic texts in conjunction with the present book is recommended for the beginner.

Surgery of the Sympathetic Nervous System. By Professor Sir James Paterson Ross, K.C.V.O., LL.D., M.S., F.R.C.S., F.R.A.C.S., F.A.C.S.; Director of the Surgical Professorial Unit, St. Bartholomew's Hospital, London. London, 1958, Baillière, Tindall and Cox, 170 pages, 19 plates. In the U.S.A., Williams & Wilkins Co., Baltimore. Price $8.00.

This monograph is written from the purview of a distinguished London surgeon whose understanding of the sympathetic nervous system has evolved through fruitful research into the impairment of its functions as well as diseases of the peripheral blood vessels. The book is characterized by an easily comprehensible style and is well illustrated.

To be sure, every shade of opinion will not find its spokesman here. For example, on page 15 the author states: ". . . it remained for Cannon to show that the ultimate function of the sympathetic system is to preserve the constancy of the fluid matrix of the body; or, in other words, that the sympathetic system is responsible for the control of the internal economy of the body, while the cerebrospinal nervous system is concerned with the reactions of the body to its external environment." This statement is not adequately convincing because the hypothalamus influences the secretion of the antidiuretic hormone which influences the electrolyte and water content of

the extra- and intracellular spaces. This same region of the central nervous system influences appetite and thirst and, in turn, the fluid matrix of the body. Although technical in nature, such considerations are important.

Sir James' book is not only recommended to the beginner but it is of value to everyone who wishes to apply physiologic concepts of the autonomic nervous system to clinical problems. The surgeon's points of view are emphasized, of course, but unfortunately fail to include sufficient emphasis of the opinions of the internists. This is to be expected but must be considered by the reader when studying Sir James' books.

The Cerebrospinal Fluid: Production, Circulation, and Absorption. Ciba Foundation Symposium. Edited by G.E.W. Wolstenholme and Cecilia M. O'Connor, Boston, 1958, Little, Brown and Company, 335 pages. Price $9.00.

This is the official record of a symposium held in May, 1957, in London, England, under the auspices of the Ciba Foundation. Each contribution is contained in a separate chapter, together with a detailed record of the informal discussion which followed. This latter addition helps considerably to evaluate each paper critically.

The first five papers are related to anatomic considerations of the structures involved in the CSF circulation. Important here are the electron microscopic observations of microvilli projecting on the surface of the choroid plexus, suggesting active function.

The second group of papers are concerned more directly with observations on the circulation of the CSF and the blood-brain barrier. The recent information afforded by experiments with radioactive isotopes has been put in its proper perspective. While these results originally suggested a rather generalized formation of CSF along the whole neuraxis, they have been interpreted more cautiously by the contributors to this volume, who favor the more classic interpretation of CSF formation, that of a product of active secretion plus some features of a dialysate, originating largely from the choroid plexus.

Much of the discussion on the blood-brain barrier has failed to take into account the recent observations of electron microscopists that there is, in fact, no real extracellular space in the brain. The blood-brain barrier seems to be the vascular endothelium and the surface of the nerve cell itself.

The final group of papers are concerned with pathologic alterations of CSF flow. Two interesting contributions are the increased CSF production related to vitamin A deficiency and the importance of the pulsatile effect of cerebral blood flow on the production of subarachnoid cysts. A brief note on complications of experimental spinal anesthesia in the cat adds little to the knowledge of CSF mechanisms.

The volume closes with a general discussion and summing up. An index is provided.

The book appears to be directed mainly to people actively engaged in research and teaching in the neurological sciences. It offers little information that would be of practical value to the internist in the management of the usual neurological problem which he is likely to meet in his practice.

Die klinische Physiologie des kleinen Kreislaufs. By Denis F. J. Halmagyi, Jena, 1957, Gustav Fischer Verlag, 252 pages, 45 illustrations.

In no other area of cardiovascular research has the progress in the last decade been more rapid than in that pertaining to the pulmonary circulation, although the clinical significance of the pulmonary circulation has been recognized for a long time. Only quite recently has the pulmonary circulation become accessible to direct measurement, owing to the development of heart catheterization, application of isotopes, and some other methods. The author has taken part in the experimental work involved in this development, and his findings are an important feature of the monograph. However, even more valuable is the comprehensive review of all aspects of the subject, documented by a bibliography of 1,693 references. This list of references alone, among them many from the European literature not sufficiently known in the United States, would make

this volume worth-while for any cardiologist and nearly indispensable for anyone actively engaged in pulmonary circulatory research. The book, published in 1957, is quite up to date on an international scale, in so far as this is possible in a field in which developments are so rapid.

The short, but most interesting historical introduction (I, pp. 1-7), tracing the history of pulmonary circulation back over 2,000 years, and illustrated with drawings of Galenus and Leonardo da Vinci, is followed by chapters on the anatomy (II, pp. 8-13) and physiology (III, pp. 14-61) of the pulmonary circulation, including methods as well as physiological regulations. A short chapter (IV, pp. 62-66) is devoted to the pulmonary circulation in the embryo and newborn. In the second and larger part of the book (Chapters V to XI, pp. 62-193) the author reviews pathology and clinical aspects: pulmonary hypertension, diseases of the pulmonary artery and smaller pulmonary arteries, congenital defects, cor pulmonale, secondary pulmonary hypertension, and pulmonary edema.

In view of the thorough documentation, the text is condensed, but is well presented. The book is undoubtedly timely. The reviewer agrees with the preface of Prof. Dr. Hetenyi, "The best recommendation for the book is the book itself."

Announcements

Dr. Louis H. Bauer, Secretary General of The World Medical Association, announced today that the Council of the Association meeting in Sydney, had appointed Dr. John M. Bishop of Bellevue, Washington, as Deputy Secretary General of The World Medical Association.

Dr. Renaud Lemieux, of Quebec, Canada, was elected at the 35th Council Session of The World Medical Association in session in Sydney, Australia, March 25 to April 5, 1959, to fill the casual vacancy as President-Elect of the Association for the term 1958-1959. Dr. Lemieux is Professor of Medicine at Laval University.

A Course in Electrocardiographic Interpretation for Graduate Physicians will be given at the Michael Reese Hospital by Louis N. Katz, M.D., and Alfred Pick, M.D., and associates. Dr. Katz and Dr. Pick are Director and Associate Director, respectively, of the Cardiovascular Department. The class will meet daily from 9:00 A.M. to 5:00 P.M., August 17 through 29, 1959.

Further information and a copy of the lecture schedule may be obtained upon application to Miss Beverley Petzold, Secretary, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago 16, Ill.